Adherence to antiretroviral treatment in selected rural and urban communities in South Africa

Strengthening understanding of effective adherence strategies for first-line and second-line antiretroviral therapy (ART) in selected rural and urban communities in South Africa

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Therapietrouw aan antiretrovirale behandelingen in geselecteerde plattelands- en stedelijke gemeenschappen in Zuid-Afrika

Versterking van het begrip van effectieve therapietrouwstrategieën voor eerstelijns- en tweedelijns antiretrovirale therapie (ART) in geselecteerde plattelands- en stedelijke gemeenschappen in Zuid-Afrika
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CHAPTER 1

GENERAL INTRODUCTION

In 2020, it was estimated that 38,4 million people were living with HIV (PLHIV) globally, with over 25,8 million in Sub-Sahara Africa alone [1,2]. While only 12% of the world's population lives in sub-Saharan Africa, this region accounts for over 70% of all PLHIV [1]. Global efforts have managed to reverse the extent of the HIV pandemic. This was achieved with a successful introduction of treatment for HIV in the late 1990s [3]. The use of antiretroviral therapy (ART) for the treatment of HIV has managed to change the HIV/AIDS landscape completely, by drastically decreasing the mortality rates of HIV-infected people and reducing HIV transmission [3,4]. The number of AIDS-related deaths has been reduced by 75% since its peak in 2004, from 2,5 million to 630,000 in 2022 [5].

Over four decades into the HIV pandemic, HIV remains a chronic condition with no curative treatment. However, the evolution of ART has significantly improved immunologic function and reduced HIV-related morbidity and mortality of PLHIV [6]. In addition, literature and clinical evidence show that ART is critical for maintaining HIV viral load (VL) suppression [6]. The provision of ART to people with HIV has continued to be scaled up, with an estimated 24.5 million people with HIV taking ART globally in 2019 [7]. South Africa contributes about 20% (4,8 million) of the global number of HIV-positive people accessing ART [1,2,7].

ART uptake and predictors of virological failure and loss-to-follow-up (LTFU)

Many countries, including South Africa, follow the World Health Organization (WHO) recommendations for first-line and subsequent-line ART [8]. South Africa replaced stavudine (d4T) with tenofovir disoproxil fumarate (TDF) in 2010 and has transitioned from efavirenz (EFV)-based first-line treatments and protease inhibitor (PI)-based second-line treatments to dolutegravir (DTG)-based regimens; all regimens include emtricitabine (FTC) or lamivudine (3TC) [9].

Despite the prescription of better tolerable regimens and a strengthened HIV program, in 2019 an estimated 15%–20% of people on first-line ART and up to 30% of people on second-line ART in the South African HIV treatment program experienced virological failure [10,11]. Further, up to approximately 40% of people on first-line ART and up to 20% of PLHIV on second-line ART were lost to follow-up (LTFU). LTFU refers to those patients who missed their clinic appointment by over 90 days or did not collect their ART without being confirmed as having died or transferred out [11–13]. Therefore, identifying factors that predict virological failure, and LTFU on either first-line or second-line ART, will facilitate the development of mitigation adherence intervention strategies in these groups. In addition, identifying patients with possible indicators of virological failure could facilitate targeted interventions to reduce the risk of switching to more complex ART regimens.

As the roll-out of ART continues to expand in South Africa, efforts are being made to optimize adherence to treatment and treatment efficacy. Suboptimal ART adherence can result in virological failure, which has adverse consequences for both individual and public health. Firstly, virological failure of ART is associated with an increased risk of disease progression and reduced survival [14,15]. Secondly, virological failure greatly increases the risk of onward transmission of HIV [10]. Finally, virological failure is often accompanied by the development of HIV drug resistance [16,17]. Drug resistance requires switching to more complex and expensive ART regimens, which have a higher pill burden, and often have less tolerable side effects [8,18].

Predictors of treatment outcomes among PLHIV on second-line ART

Despite improved ART coverage in sub-Saharan Africa, recent evidence has shown that between 8% and 23% of PLHIV will fail first-line ART by 5 years after initiation and will require switching to more complex and expensive protease inhibitor (PI) based second-line ART regimens [19–21]. Unlike in many lower-middle-income countries (LMICs), second-line ART is readily available in South Africa, although at a very high cost compared to first-line ART [12]. Also, the rate of switching to second-line ART in South Africa is substantially higher than in other LMICs [22–24]. Some studies that have reported outcomes of second-line ART in LMICs show that the proportion of adult PLHIV who experienced virologic failure varied widely from 8.3% to 41.2% at 24 months [25]. In South Africa, 23–35.6% of patients will experience treatment failure by 12 months on second-line ART [26–28].

Although the exact switch rates are unknown, it is estimated that there are over 200,000 PLHIV on second-line ART in South Africa [29,30]. This progression from first- to second-line treatment is in accordance with World Health Organization (WHO) guidelines [31]. Second-line treatment is complex, involving numerous tablets with substantial toxicity and twice-daily dosing. However, there are limited studies that explore second-line treatment outcomes, [32–34], and unlike patients on first-line ART, little is known about the clinical outcomes of patients on second-line ART. Therefore, identifying demographic characteristics and clinical factors that predict virological failure among PLHIV on second-line ART, may allow for more targeted adherence and support interventions.

Multi-level factors associated with adherence to ART

Although ample literature on adherence to ART has been available for a while, there remains a dearth of studies relating to the multi-level factors associated with adherence to treatment and processes shaping adherence behaviour, particularly in South Africa. This lends credence to the lack of understanding of the interplay between the various factors involved at different levels of influence on the treatment-taking behaviour of the ART patient.

Non-adherence to ART in sub-Saharan Africa is associated with patient-related risk factors and social determinants, including changes in daily activities, forgetting to take ART, lack of health literacy, unwillingness to take ART, unemployment, poverty, HIV-status disclosure concern, HIV-related stigma, lack of clinician trust, poor coping mechanisms and mental health problems [35–38]. The effect of these risk factors may be more profound in rural populations, as studies on barriers to care found that PLHIV in rural areas reports more severe barriers to care than those living in urban areas [39,40]. This may be of particular relevance to male PLHIV in sub-Saharan African settings, who are at increased risk of various adverse outcomes of treatment, in part stemming from lack of access to care [41–43]. Identifying high-risk socio-demographic, socio-economic, psycho-social, and clinical factors may guide focused adherence measures and the establishment of a clear adherence profile for patients on ART.

Treatment behaviours and perspectives of PLHIV on adherence to second-line ART

While the literature has reported several barriers to adherence in general, there is still a threat of elevated treatment failure due to patient-related adherence concerns amongst PLHIV who are on ART, particularly in LMICs and PLHIV on second-line ART [44]. Notably, among such populations, patient-related barriers to adherence, issues such as unstable lives that may compromise daily medication, and lack of power in treatment decision-making have been noted [45–48]. In addition, patients experiencing financial constraints and social issues such as fear of disclosure, face significant barriers in adhering to treatment and staying sufficiently healthy [49,50]. Furthermore, factors such as the selection of a person to disclose to, are also likely to influence adherence [51]. Studies conducted in South Africa reported that clients who also disclosed to a partner or close relatives were more likely to experience virological suppression compared to those who only disclosed to friends or work colleagues [52,53]. However, not much is documented about the perspectives of patients who experience adherence challenges to second-line ART [57]. It is important, therefore, to understand the different treatment-taking behaviours and perspectives of PLHIV who are on second-line ART experiencing virological failure, adherence challenges, and their recommendations to improve adherence.

Factors contributing to adherence: an overview of theoretical frameworks

Effective ART adherence support requires an understanding of the multi-level factors affecting adherence, which include socio-demographic, socio-economic, psycho-social, and environmental conditions [54]. Knowledge of these factors may be used to identify individuals at risk of non-adherence or virological failure and to identify factors that can promote ART adherence and improve patient care and programmatic outcomes. The goal is to identify suboptimal adherence and intervene before it reaches a level that results in viral load rebound or virological failure [55].

Therefore, interventions to achieve optimum adherence to ART should include monitoring of viral load, and adherence behaviours that aim to improve linkage and retention to care [55].

There are several models, each with its main focus, which could be used to explore factors at multiple levels related to adherence. Most of these models help understand the contribution of individual or patient-related factors in adherence to medication [56]. One model that is of particular significance to this study is the HIV Continuum of Care Model [55,57] (Figure 1). This model specifies the consecutive stages that individuals with HIV go through, from HIV diagnosis to achieving and maintaining viral load suppression. The subsequent stages of the HIV care continuum include diagnosis of HIV infection, linkage to HIV care, receiving HIV care (ART), retention in care, and achievement and maintenance of viral suppression [55,57]. The HIV continuum of care model also includes the option of re-engagement in the care of people who discontinued care, emphasizing the importance of forging relationships between health facilities and communities to ensure that PLHIV are reconnected to care [55,57]. The HIV continuum of care model emphasizes that optimal engagement of people with HIV in all steps along the continuum of HIV care needs to be optimized to achieve viral load suppression in the highest number of people with HIV. According to the model authors [60], the implications of poor engagement and retention in care at the individual level include delays in ART initiation, sub-optimal adherence to ART, low CD4 cell count, high viral load, and resistance to ART.

Importantly, many factors influence the ability to successfully engage PLHIV in the HIV continuum of care. These include individual risk factors such as age, sexuality, mental health, and others. Beyond these factors, there is the influence of relationships for PLHIV who are on ART with others (e.g., with an intimate partner, significant other, or with family members, peer mentors or treatment supporter and/or clinicians), community-related factors (e.g., education level, employment status, poverty, income, and social norms), health care system–related factors (e.g., distance to health facilities, health service integration), and health care policy–related factors (e.g., HIV treatment guidelines) [55,58].

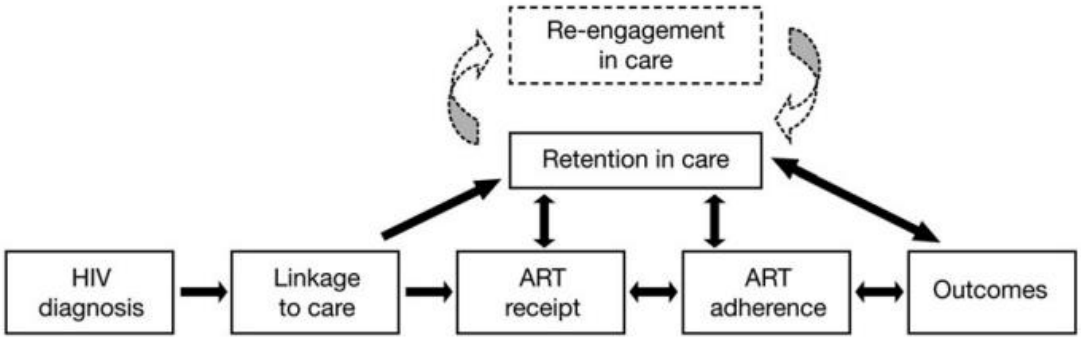

Figure 1: HIV Care Continuum Model: HIV care cascade outlining the requisite steps from HIV testing and diagnosis to achieve optimal clinical outcomes. The processes of engagement in HIV care—linkage, retention, and re-engagement. Adapted from Mugavero et al.,[55,59] and Ulett et al,.[60] *(License to reproduce this figure was obtained from Oxford University Press).*

Another noteworthy model is the socio-ecological conceptual framework of health [58,61] (figure 2). This model underscores the interplay on the health of individual characteristics, their connections to other people, and how they adapt their behaviour to the social environment. A socio-ecological perspective (figure 2) provides a framework for conceptualizing the complex interplay of individual-, relationship-, community-, healthcare system–, and policy-level factors that influence the processes of the HIV continuum of care and engagement in HIV care [59]. It gives an overview of multi-level factors that may shape various HIV-related behaviours, including those inherent in the HIV Care Continuum Model: HIV care cascade [58,59,61].

The socio-ecological framework of health understands adherence to treatment to be affected by the interaction between the individual, relationships or interpersonal, community, and the social, and related policies [62]. It categorizes related factors based on the societal level at which they exist, including at the individual level (e.g., sex, age, education, stigma, coping mechanisms), relationship or interpersonal level (e.g., intimate partners, family members, friends); community level (e.g., poverty, employment, social norms, social support) and policy level (e.g., HIV treatment guidelines that promote adherence to ART) [62,63]. The influence of individual characteristics, relationships, and community engagements particularly social support, increases engagement in HIV care and adherence to ART. Having others in one's life who provide treatment support is associated with better adherence and treatment-taking behaviour [63].

Although factors on adherence for PLHIV who are on ART have been documented, few studies have concurrently examined multiple socio-ecological factors, at the individual, relationships, community, and policy levels, along the HIV continuum of care among PLHIV who are on ART in

South Africa. Therefore, our study assesses multi-level factors along the HIV continuum of care among PLHIV who are on ART) [63]. This thesis assumes that each step of the HIV continuum of care model would be affected by socio-ecological factors at multiple levels. It also demonstrates the effect of the socio-ecological model on engagement in HIV care along the HIV continuum of care for PLHIV who are on ART.

An adapted socioecological framework provides greater depth to the myriad of layers influencing engagement in HIV care across the continuum of care [63]. The socio-ecological framework gives an overview of factors that may shape various HIV-related behaviours, including those inherent in the HIV care continuum cascade. Drawing on this multilevel socio-ecological framework of health, this thesis provides information about the influence of particular risk factors relative to others, or whether combined effects of risk factors are additive or related. Integrating two models, and multiple steps affected by factors at multiple levels, our thesis provides guidance regarding facilitators and barriers to adherence, and how adherence intervention strategies can target individual, patient relationships with others, community, and healthcare policy levels.

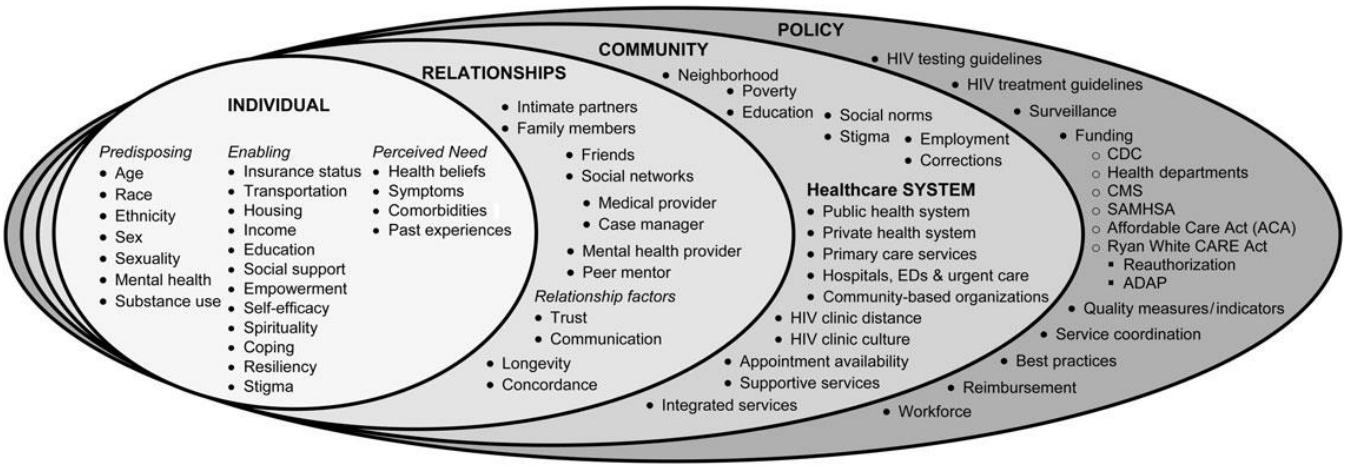

Figure 2: A socioecological framework that sketches the layers of individual, relationship, community, healthcare system, and healthcare policy factors that influence the processes of engagement in care. Abbreviations: ADAP, AIDS Drug Assistance Program; CARE, Comprehensive AIDS Resources Emergency; CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare and Medicaid Services; ED, emergency department; HIV, human immunodeficiency virus; SAMHSA, Substance Abuse and Mental Health Services Administration [58]. *(License to reproduce this figure was obtained from Oxford University Press).*

Intervention strategies to improve adherence to ART

In the efforts to address adherence to treatment to treatment; behavioural and psychological factors, education, integrated care, and patient self-management interventions have been explored [64,65]. This includes behavioural rehabilitation provided by health providers to patients, integration of psychosocial support within health programs, and patient's knowledge about the medication and their overall satisfaction with the treatment [66–68]. However, no single intervention is deemed sufficient to ensure that high levels of treatment adherence are maintained, not only for HIV but for other chronic conditions and/or non-communicable diseases as well [35,64–66]. While HIV remains the leading cause of death in sub-Saharan Africa, there has been a rise in the burden of non-communicable diseases, particularly hypertension and diabetes mellitus in sub-Saharan Africa in recent years [69–72]. Therefore, understanding adherence to related medication for these chronic conditions should also be a priority. Also, there remains a need to strengthen and tailor different intervention strategies to different barriers to adherence for these chronic conditions as well [35].

In general, and in South Africa specifically, there is a lack of reported knowledge about the effectiveness and impact of strategies to promote adherence in individuals who are taking chronic medication. This pertains particularly to young patients, males, and those experiencing severe treatment-related side effects. [53,73]. Until 2017, minimal ART adherence strategies were employed in South Africa, mostly consisting of routine blood monitoring, and targeted adherence counselling by health care providers and adherence clubs [74–76]). Adherence clubs comprise clinically stable patients on ART who meet at health facilities or designated community venues in groups of up to 30 patients every 2 to 3 months to receive group counselling, brief symptom screening, and prepacked medications [74,77]. However, the efficacy of these abovementioned interventions has not been fully assessed.

As it stands, in South Africa various measures aimed at improving patient adherence to treatment have been implemented. There has been a greater emphasis on the importance of interventions such as psycho-social support, health literacy, and knowledge of ART benefits [82–85]. One way in which this has been put into action is adherence counselling provided by facility-based healthcare workers. Another focuses on patients receiving adherence or treatment support from family or friends, or through community-based programs. At times, impersonal strategies like alarm clock or SMS reminders, pill counts, and medication and drug level monitoring have been employed. Differentiated Models of Care like adherence clubs, pick-up points, and multi-month dispensing have also been pushed forward [86,87]. In addition, the South African Department of Health also advocated not only compliance with standard treatment guidelines but also collecting and monitoring the usage of data to promote overall adherence to treatment [85,88,89].

Adherence programs have evolved to include technology. Some studies have assessed the efficacy of digital health or mobile health interventions to promote adherence to ART, via telephone counselling and text message reminders [66,68,90]. Findings from these studies have emphasized that interventions that use digital technology to promote health have the potential to facilitate adherence education, self-management, and treatment-related support. While research is scarce on digital interventions to improve adherence in sub-Saharan Africa, there is evidence from other regions that electronic diaries, electronic drug monitors, and electronic messages can improve treatment adherence [35,82,88,91]. Notwithstanding the positive impact the use of digital health applications could have in promoting treatment adherence, its application has thus far been limited in sub-Saharan Africa [88,89,92–94].

Research aim and research questions

This thesis aims to assess the barriers and facilitators to adherence for patients receiving first-line and second-line ART and evaluate adherence strategies utilized in rural and urban communities in South Africa.

Our study adapted the socio-ecological framework (Figure 2) in conceptualizing the complex interplay of individual-, relationships-, community- and policy-level factors that influence adherence to ART across the overall continuum of the HIV care model (Figure 1) [59]. Therefore, the socio-ecological framework and HIV care continuum model served as the conceptual frameworks in our study to understand factors affecting treatment adherence at different levels and also guide strategies to improve ART adherence.

The thesis addresses the following specific research questions:

1. What is the uptake rate of ART, and the individual level factors associated with virological failure and being lost to follow-up in PLHIV taking first-line and second-line ART in urban communities?
2. What are the individual-level factors that predict virological failure, low CD4 count, and retention in care for patients on second-line ART in urban communities?
3. What are the individual, relationship or interpersonal, and community level factors associated with self-reported adherence, pill count, and virological failure to first-line and second-line ART in rural communities?
4. What are the different treatment-taking behaviours and perspectives on adherence to ART between virally suppressed and unsuppressed patients on second-line ART in urban communities?
5. What treatment adherence strategies and interventions have been implemented and evaluated in sub-Saharan Africa for ART, hypertension, and Diabetes Mellitus?

Outline of the thesis

Chapter 2 is a protocol paper, detailing the rationale, study aims, research designs, and methods employed in the studies reported in this thesis. Using learnings from previously published literature, our study elaborated and adapted a multi-level socio-ecological framework to investigate factors at multiple levels and their interplay including individual, relationship or interpersonal, and community-level factors that may affect adherence to ART. We explored the different factors within overarching categories that act either as barriers or facilitators of adherence to ART.

In chapter 3, we describe the changes in ART regimens and uptake of ART and also present a retrospective analysis of individual-level factors that predict virological failure and LTFU in a large cohort of HIV-infected adult patients who were initiated on first-line and second-line ART between April 2004 and February 2020 in Johannesburg region F, South Africa. Johannesburg Region F sub-district (inner-city) is one of seven sub-districts of the Johannesburg Metropolitan Municipality in Gauteng Province, South Africa. The inner city is densely populated, consisting of very highly mobile communities. The region has about 15% of the 5 million people who live in the city of Johannesburg [97]. The inner city is uniquely complex and has undergone major demographic, social, and economic shifts over the last few years [97]. Almost 1 in 3 of its inhabitants are immigrants from nearby countries such as Zimbabwe, Lesotho, and Mozambique, while the majority of its population comes from other provinces as well [97]. According to the routine data, Johannesburg Region F has closer to 100,000 PLHIV who are on ART [98]. Even though the region has reported higher viral load suppression rates, in contrast, it has reported higher LTFU rates of up to 40%, suggesting the need to prioritize interventions to promote adherence to treatment and retention in care in this region [99]. Data for this study are derived from TIER.Net, the ART monitoring and evaluation system of the South African National Department of Health. This chapter further assesses ART status and CD4 count as covariates of retention in care and virological failure. A total of 123,002 records of people with HIV taking ART (first-line regimen and second-line regimen) were included in the analyses between outcome variables (VL and retention in care status) and individual level factors (age at start of ART, current age, sex, duration on ART, baseline CD4 count, regimen combination, levels of health facility). Our findings from this study noted some of these factors for targeting HIV treatment program strengthening.

The study reported in chapter 4 used TIER.Net data to follow a cohort of patients on second-line ART between 2014 and 2015. Second-line ART is complex, and it involves numerous tablets with substantial toxicity and twice-daily dosing [100]. Patients failing on second-line ART have very limited further treatment options available in the public sector [100]. Switching patients who experience failure of first-line treatment to second-line regimens has been the standard policy in the South African public health setting since the inception of the ART program in 2004 [11].

However, not much research has been done to assess the long-term clinical outcomes of patients on second-line treatment. It is estimated that approximately 5% of all PLHIV who are on ART in South Africa have been switched to the second-line regimen. Of patients on second-line treatment, 20%-30% are thought to experience treatment or virological failure [10,101]. Moreover, in the face of creating a less complex second-line ART regimen, little is known about what individual factors are related to virological failure, low CD4 cell count, and retention in care among PLHIV who are on second-line ART. In this retrospective cohort study of 825 records, we assess the virological failure, immunological outcomes, and retention in care in the patients who switched to second-line ART in public health facilities in Johannesburg. The study reported in chapter 4 identifies individual and community-level factors that predict virological failure, low CD4 cell count, and LTFU among people living with HIV who are on ART. These findings may guide future targeted ART adherence and support interventions.

For the study reported in chapter 5, we used the data from the Intensified Treatment Monitoring Strategy to Prevent Accumulation of Drug Resistance study (ITREMA; Clinicaltrials.gov NCT03357588). ITREMA was an open-label randomized clinical trial evaluating different treatment monitoring strategies for first-line ART, which ran from June 2015 to January 2019 at the Ndlovu Medical Center in the rural area of Elandsdoorn, Limpopo Province, South Africa [102]. We conducted a prospective cohort study as a sub-study to assess ART non-adherence and virological failure among participants in the ITREMA trial. PLHIV who live in rural settings are often severely affected by disadvantaged socio-economic status, limited access to healthcare services, and poor infrastructure and healthcare resources. These populations may therefore have unique barriers and facilitators of adherence to HIV treatment. In the ITREMA sub-study, we set out to perform a comprehensive assessment of psychosocial, behavioural, and socio-economic risk factors for non-adherence and virological failure in PLHIV accessing care in a rural community. A well-characterized cohort of 501 participants on ART received long-term follow-up for 96 weeks, during which markers of adherence and virological suppression status were periodically assessed. In this study, we identify several demographic, socio-economic, and behavioural risk factors for non-adherence and virological failure and show that there is a limited overlap of markers of adherence with virological failure.

In chapter 6, we report a study of the perspectives on treatment adherence of two separate groups of PLHIV who are on second-line ART to understand differences in treatment-taking behaviour: those whose viral load was sustainably suppressed, and those whose viral load was detectable. This study shares the perspectives of patients experiencing virological failure, adherence challenges, and patients' recommendations to improve adherence, as not much is documented about the perspectives of patients who experience adherence challenges [103]. To address this knowledge gap, we undertook a cross-sectional study between July and August 2018

in a sub-population of 149 patients receiving second-line ART in five public health facilities in Johannesburg. This study identifies a few demographic risk factors associated with virological failure. The study emphasizes the importance of improving patients' efficacy and knowledge about ART, adherence to ART, and motivation to continue ART use despite any medication-related challenges. This study also provides information on the treatment adherence strategies recommended by these patients.

Chapter 7 reports a systematic review assessing the impact of treatment adherence interventions for chronic conditions (ART, hypertension, and diabetes mellitus) in sub-Saharan Africa. Non-communicable diseases are the leading cause of death worldwide, contributing 41 million deaths each year, equivalent to 71% of all deaths globally [69,104]. Non-communicable diseases are set to overtake communicable, maternal, neonatal, and nutritional diseases combined as the leading cause of mortality in sub-Saharan Africa by 2030 [69]. Intervention strategies are therefore needed to curb the burden of non-communicable diseases in the region [69][104]. This chapter emphasizes the need to strengthen and tailor different intervention strategies to different barriers to adherence for chronic conditions. In this review of 77 articles, we assess treatment adherence interventions for ART, hypertension, and diabetes mellitus in sub-Saharan Africa, which provides valuable comparisons and context to adherence intervention strategies for these chronic conditions in sub-Saharan Africa. This review followed the registered protocol on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019127564) [105]. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[106] and different tools for assessment of quality and risk of bias [107–110] this systematic review describes and reports on intervention strategies that can improve adherence to medication for chronic conditions. Our study reports on the effectiveness or the performance of these treatment adherence strategies and interventions.

Chapter 8 discusses the evidence presented in all the study chapters, provides context to the findings about the research questions, and discusses its implications for future research along with recommendations. Thereafter, the strengths, limitations of this thesis, and directions for future research are also discussed.

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CHAPTER 2

Study protocol: Strengthening understanding of effective adherence strategies for first-line and second-line antiretroviral therapy (ART) in selected rural and urban communities in South Africa

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ABSTRACT

Multiple factors make adherence to antiretroviral therapy (ART) a complex process. This study aims to describe the barriers and facilitators to adherence for patients receiving first-line and second-line ART, identify different adherence strategies utilized and make recommendations for an improved adherence strategy. This mixed method parallel convergent study will be conducted in seven high volume public health facilities in Gauteng and one in Limpopo province in South Africa. The study consists of four phases; a retrospective secondary data analysis of a large cohort of patients on ART (using TIER.Net, an ART patient and data management system for recording and monitoring patients on ART and tuberculosis (TB)) from seven Johannesburg inner-city public health facilities (Gauteng province); a secondary data analysis of the Intensified Treatment Monitoring Accumulation (ITREMA) trial (a randomized control trial which ran from June 2015 to January 2019) conducted at the Ndlovu Medical Center (Limpopo province); in-depth interviews with people living with Human Immunodeficiency Virus (PLHIV) who are taking ART (in both urban and rural settings); and a systematic review of the impact of treatment adherence interventions for chronic conditions in sub-Saharan Africa. Data will be collected on demographics, socioeconomic status, treatment support, retention in care status, disclosure, stigma, clinical markers (CD4 count and viral load (VL)), self-reported adherence information, intrapersonal, and interpersonal factors, community networks, and policy level factors. The systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting and Population, Interventions, Comparisons and Outcomes (PICO) criteria. Analyses will involve tests of association (Chi-square and t-test), thematic analysis (deductive and inductive approaches) and network meta-analysis. Using an integrated multilevel socio-ecological framework this study will describe the factors associated with adherence for PLHIV who are taking first-line or second-line ART. Implementing evidence-based adherence approaches, when taken up, will improve patient's overall health outcomes. Our study results will provide guidance regarding context-specific intervention strategies to improve ART adherence.

INTRODUCTION

Inconsistent adherence to treatment is a contributing factor to poor health outcomes of people affected by numerous health conditions, including HIV, tuberculosis, diabetes mellitus (DM) and hypertension [1–3]. The World Health Organization (WHO) defines adherence as the degree to which a patient is able to follow a treatment schedule and take medication at recommended times [4–6]. In the context of HIV, lapses in adherence to medication can lead to the development of viral rebound, which can result in immunosuppression and viral resistance [4,7–9].

WHO recommends the use of the HIV drug dolutegravir (DTG) as the preferred first-line and second-line ART treatment regimens for all populations due to its formidable resistance barrier and improved tolerability [10–12]. Despite the advantages of this first-line regimen, in South Africa between 20%-30% of patients with HIV experience clinical, immunological or virological failure from first-line ART due to lapses in adherence [13–15]. This is a concern because of the clinical and cost implications attached to treatment failure [16,17].

Adherence to ART is a complex process that is affected by multiple factors, and numerous studies have attempted to establish what the barriers and facilitators of ART adherence are [18–20]. Individual-level factors such as age, sex, ethnicity, HIV status disclosure and forgetfulness, have been reported as important in predicting ART adherence [21]. However, using individual-level factors one is only able to report a limited proportion of the variability in nonadherence [22]. Good interpersonal relationships between patients and care givers or treatment supporters including healthcare providers, an intimate partner, family members, and friends have been reported as predictors for good adherence [22,23]. In contrast to intrapersonal and interpersonal factors, the community level factors such as poverty, HIV related stigma and discrimination against patients on ART introduce barriers to ART adherence [24]. Additional to community level factors, awareness of healthcare policy level factors like HIV treatment guidelines, policies, and best practices are imperative in ensuring good adherence and maintenance of the continuum of care [25].

Conceptual framework

Various studies have demonstrated that there are many factors that play an important role in maintaining adherence behaviour [26–29]. These factors have been explored using several models, including: 1) Anderson's Health Care Utilisation model [30], which is a framework that considers predisposing factors (individual' own personality and behaviour), enabling factors (patient and health provider relationship, community education) and need factors (patient's beliefs, alternative medicine treatment options, community support); 2) the Dahlgren-Whitehead 'rainbow model' [31], a model that builds the relationship between the individual, the environment they live in and health; 3) Information-Motivation-Behavioural skills model (IMB

model) [32–34], a model that views adherence behaviour as a function of the interrelations between adherence-related information, motivation, and behavioural skills; 4) the socio-ecological conceptual framework [35,36], which takes into consideration the individual, and their connections to other people, and how they adapt their behaviour to the social environment. This model suggests that an individual's behaviour is cohesive in a dynamic network of intrapersonal, interpersonal characteristics, community features and existing health policies [35,36]. Our study will adapt the socio-ecological conceptual framework to investigate multilevel and interactive factors such as individual/intrapersonal, interpersonal, community, and health policy level factors that affect adherence to ART (Fig 1). It will explore the different aspects of these factors that act either as barriers or facilitators of adherence to ART.

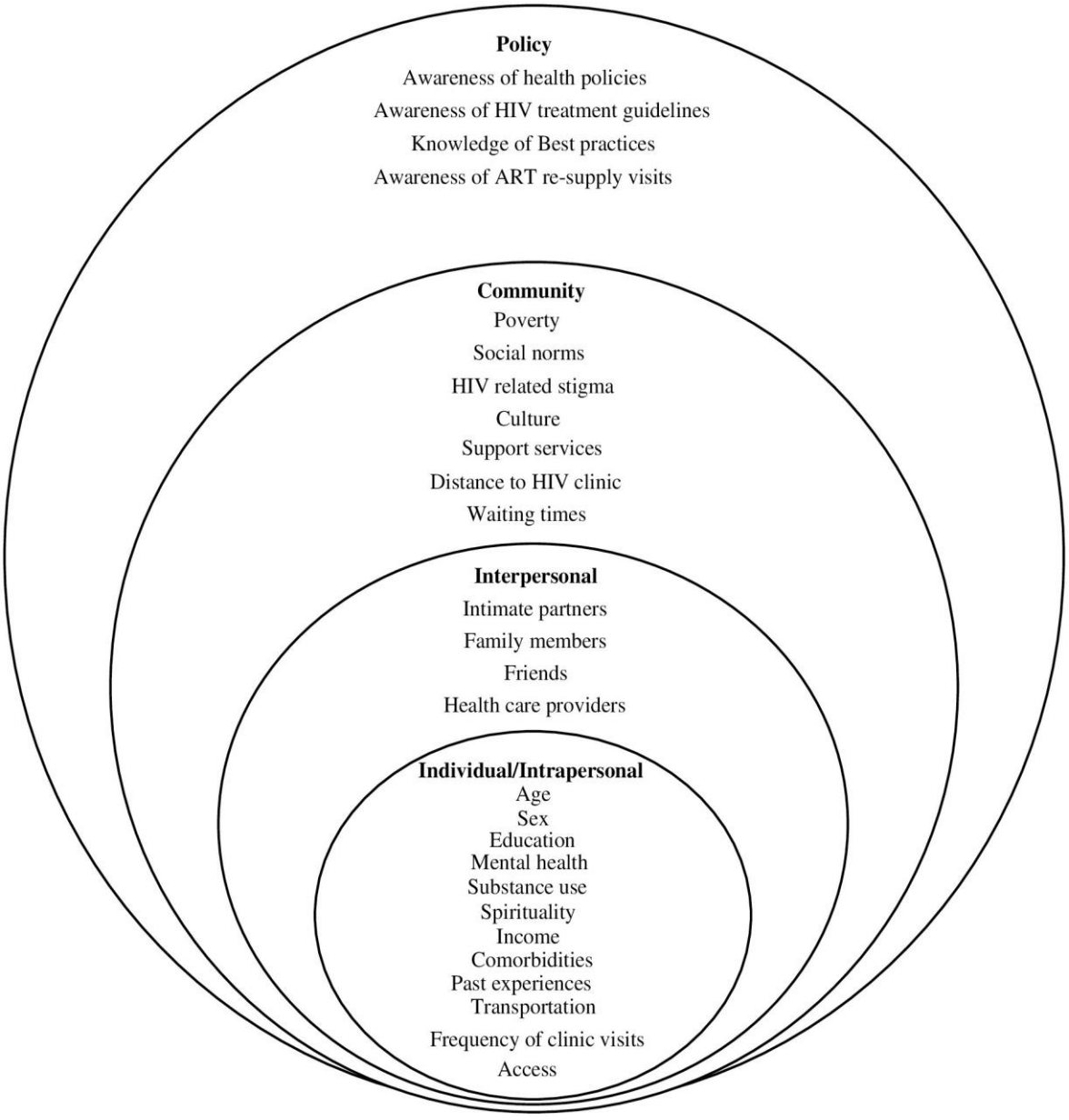

Figure 1. An adapted socio-ecological framework. An adapted socio-ecological framework that depicts the layers of individual, relationship, community, and healthcare policy level factors which influence the processes of treatment adherence and retention in care [36].

Intrapersonal level factors: The intrapersonal level of the socio-ecological conceptual framework comprises individual knowledge, attitudes, beliefs, perceptions, and skills that influence behaviour [35]. It further includes age, sex, income, mental health, education, substance use, spirituality, comorbidities and past experiences [36].

Interpersonal level factors: Here the participant's social network or relationships with other people including family, friends, peers, intimate partner and health care providers [35] are included. This level also highlights trust and communication as factors that builds a relationship between patients and care givers or treatment supporters [25].

Community level factors: The components of the community-level factors that may influence patient's adherence to ART incorporate cultural views and social norms towards ART access, HIV related stigma, poverty, and available support services within the community [36].

Policy level factors: The public policy level is shaped by local, and government laws regarding access and adherence to ART. The socio-ecological conceptual framework reports on awareness of macro level factors which includes health policies, HIV treatment guidelines and best practices, [22,36].

Research gap

Although ample literature on adherence to ART has been available for a while, there remains a dearth of studies relating to the multi-level factors associated with adherence to treatment and processes shaping adherence behaviour, particularly in South Africa. This lends to the lack of understanding of the interplay between the various factors involved at different levels of the treatment taking behaviour of the ART patient.

In South Africa specifically, there is lack of reported knowledge about the effectiveness and impact of strategies currently employed to promote adherence in people living with HIV (PLHIV) who are taking ART (particularly young patients, males, and those experiencing severe treatment related side effects) [37,38]. Unfortunately, there are no quantitative studies of combination ART in South Africa (and even sub-Saharan Africa more generally) that have used a social-ecological perspective or approach. This is despite the understanding that patients on ART require comprehensive adherence strategies and strict viral load monitoring [39,40].

Until 2017, there were minimal related treatment adherence strategies (routine blood monitoring, targeted adherence counselling, and adherence clubs [41–43]) employed by the South African government [41]. However, effectiveness of these interventions have not been widely reported on. Additionally, the patients' perspectives seem to be given little consideration in the adherence

intervention development and implementation. It is therefore important to assess effectiveness of existing strategies from the perspectives of PLHIV taking ART in order to recommend and develop relevant and acceptable strategies to patients [44,45]. This is evidenced in a study conducted in Malawi which highlighted how critical it is for health programmers to prioritize adherence viewpoints from patients as part of strengthening the clinical monitoring strategy used [46].

Rationale for the study

Consistent high levels of adherence to HIV medication are important for viral suppression, consequently preventing resistance to ART and progression of the illness [47]. According to the socio-ecological framework, numerous levels of factors affect patients' adherence to treatment [25]. Therefore, a multilevel socio-ecological framework will provide information about the influence of particular risk factors relative to others, or if combined effects of risk factors are additive or related. The socio-ecological framework will serve as the conceptual framework in our study in order to understand factors affecting treatment adherence at different levels and also guide strategies to improve ART adherence.

Aim: To describe the barriers and facilitators to adherence for patients receiving first-line and second-line ART and different adherence strategies utilised.

Overarching hypothesis: A socio-ecological framework combined with multi-model data collection will identify the barriers and facilitators to ART adherence and retention in care for PLHIV needed to strengthen adherence interventions.

Research questions and hypotheses

1. What are the demographic characteristics and clinical indicators associated with virological failure and being lost to follow-up (LTFU) in PLHIV taking first-line and second-line ART in urban communities?

Hypothesis: Demographic and clinical characteristics are associated with virological failure and being LTFU in patients on ART from complex, and highly mobile urban communities.

2. What are the intra-and inter-personal factors (demographic, socio-economic characteristics), social and community level factors (poverty, social norms, HIV related stigma, culture), structural factors (health systems, support services) and clinical indicators associated with self-reported adherence, pill count and virological failure to first-line and second-line ART in rural communities?

Hypothesis: Individual and community level factors are associated with self-reported nonadherence, suboptimal pill count, and virological failure in patients on ART in the rural setting.

3. What are the perspectives of virally suppressed and unsuppressed first-line and second-line ART patients about treatment adherence in selected urban and rural communities?
a. Are there any differences between people receiving first-line and second-line ART?
b. Are there any differences in treatment taking behaviours between virally suppressed and unsuppressed ART patients?
c. What do virally suppressed and unsuppressed ART patients recommend as adherence strategies?
Hypothesis: In South African communities, treatment taking behaviour, perceptions of adherence, and recommendations for adherence interventions differ between PLHIV who are virally unsuppressed and those who are virally suppressed.

4. What treatment adherence strategies and interventions have been implemented and evaluated in sub-Saharan Africa for HIV, hypertension, and DM?
Hypothesis: There are no differences in the effectiveness of adherence interventions implemented in sub-Saharan Africa for HIV, hypertension, and DM.

MATERIALS AND METHODS

Study design

The study will employ a mixed method parallel convergent approach conducted in four phases (I-IV). Due to the different approaches for each study objective, we present the study methods based on each objective. While the studies will employ their own separate methods, all the results will be converged/collated into a single discussion to provide recommendations for adherence strategies that can be rolled out in South Africa.

Materials and methods: Phase I

Objective 1: Assess demographic characteristics and clinical indicators associated with virological failure and LTFU in first-line and second-line patients in an urban community.

Study design

The study will employ a quantitative retrospective cohort study using secondary data analysis of data on people with HIV taking ART (18 years and older) recorded in the TIER.Net database. TIER.Net is the monitoring and evaluation system used by the South African Department of Health for ART patient and data management. It comprises limited demographic information and all treatment and laboratory information from the time of commencement on HIV treatment. This is elaborated on in the data collection section. The South African Department of Health started providing ART in the public health setting on 01 April 2004. From TIER.Net, we will extract a list of all patients who were initiated on ART from 01 April 2004 to 29 February 2020 in the urban setting (city of Johannesburg region F). The cut-off period of 29 February 2020 was chosen to give ART

cohorts a minimum of a 12-month follow-up during which a full clinical assessment could be completed as per guidelines.

Study setting

This study will be conducted in seven health facilities in the city of Johannesburg region F. This includes all levels of care

1. Primary Health Care: Jeppe Clinic, Malvern Clinic, Rosettenville Clinic, Yeoville Clinic
2. Community Health Centre: Hillbrow Community Health Center (HCHC)
3. Hospitals: Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and South Rand Hospital (SRH)

Sampling/Sample size

For this study, all records of people with HIV who were ever initiated on ART between 01 April 2004 (the inception of the South African national HIV treatment programme in the public health setting) and 29 February 2020 from the seven public health facilities will be included. Based on the TIER.Net database, about 130 000 adult patients were initiated on first-line and second-line ART in the seven facilities selected in the city of Johannesburg region F.

Data collection

Data will be extracted from the TIER.Net database (as an MS Excel export file). TIER.Net captures demographic information such as patient age, sex, facility name and contact details and also HIV specific information such as HIV diagnosis date, ART start date, regimen at baseline, ART visit dates, CD4 count, viral load done and viral load suppression. The system also records all treatment related information, including ART switch. All these variables will be extracted (see S1 Appendix study codebook). The data will be exported to STATA 15.1 for data cleaning and analysis. Records with missing data will be excluded in the final analysis. This will be after conducting all necessary data quality checks, verifications, and triangulations with other data sources.

Outcome: VL count is categorized into suppressed (<1000 copies/ml) or unsuppressed (≥1000 copies/ml) [48,49]. The status on retention in care for patients will be categorized into active in care, LTFU, transferred out, or recorded dead. For this study, LTFU is defined as having missed a scheduled medical appointment by 90 days or more, as defined by the South African Department of Health [50].

Data analysis

Data will be coded and analysed using STATA version 15.1. Tests of association (Chi-square and t-test) between outcome variables and selected demographics characteristics and clinic indicators will be conducted. Outcome variables will include viral load detectability and retention outcomes

(active in care, transferred-out, lost to follow-up and dead). Regression analysis, univariate and multivariate analyses between variables will be built for outcome variables to identify independent predictors. Variables such as age, sex, health facility, baseline regimen, ART start date, baseline CD4 count, most recent CD4 count, ART visit dates, and months on ART will be considered as predictor variables or independent variables. Analysis will include survival analysis which will consider different entry time points into the ART program. Subsequently, patients will not be grouped all together but will be followed up in a 12-month interval when measuring the outcomes (virological failure and lost to follow up).

Materials and methods: Phase II

Objective 2: Assess socio-demographic and psychosocial associated with adherence (self-reported adherence, pill count and virological failure) in patients on first-line and second-line ART in a rural community.

Study design

This cohort study using secondary data analysis will be conducted as a sub-study of the Intensified Treatment Monitoring Accumulation (ITREMA) study (Clinicaltrials.gov Identifier NCT03357588) [51]. The ITREMA database will be used to extract ART information. ITREMA is an open-label randomised clinical trial evaluating different treatment monitoring strategies for first-line ART, which ran from June 2015 to January 2019 [51]. ITREMA was conducted at the Ndlovu medical centre in Limpopo province, South Africa. The ITREMA study enrolled adult PLHIV and assessed an intensified HIV-treatment monitoring strategy in a randomised comparison with a control group receiving standard-of-care HIV treatment in accordance with the South Africa National Department of Health guidelines.

Study setting

Patient enrolment for the ITREMA trial was done between June 2015 and August 2017 at the Ndlovu Medical Centre in Elandsdoorn, Limpopo Province, South Africa.

Sampling/Sample size

All the records from ITREMA database will be used. There are 501 ART patients in the ITREMA database.

Data collection

Data will be extracted from the ITREMA databases. The ITREMA database contains fields for socio-demographics and psychosocial characteristics. The control variables include sex, age, level of education, employment status, sources of income, household members, food security, mental

health, HIV self-efficacy and HIV related stigma (see S1 Appendix study codebook and S6 Appendix ITREMA questionnaire). The data will be exported to STATA 15.1 for data cleaning and analysis.

Outcome: Self-reported non-adherence will be measured using three items from the ACTG questionnaire [52]: "How often do you have difficulty in taking your medication on time?, with responses given on 4-point scale (All the time, Most of the time, Rarely, Never), "On average how many days per week would you say that you missed at least one dose of your medication?", with responses given on a 6-point scale (every day, 4–6 days per week, 2–3 days per week, Once a week, Less than once a week, Never), and "When was the last time you missed taking any of your medications?", with responses also given on a 6-point scale (Past week, 1–2 weeks ago, 2–4 weeks ago, 1–3 months ago, More than 3 months ago, Never) (see S6 Appendix ITREMA questionnaire). Responding 'never' to all three questions will be taken to indicate good self-reported adherence. Suboptimal adherence measured using pill count is defined as a pill count <95%. This threshold is aligned with the WHO cut-off, which considers a pill count ≥ 95% as good adherence for patients taking ART [53]. Virological failure will be defined as viremia ≥1000 copies/ml within 96 weeks of follow-up [48,49].

Data analysis

Data will be coded and analysed using STATA version 15.1. Tests of association (Chi-square and t-test) between outcome variables and selected socio-demographics and health related characteristics will be conducted. Outcome variables will include (but not limited to) viral load detectability, retention outcomes (active in care, transferred-out, lost to follow- up and dead), side effects and treatment interruptions (stop and restarting treatment). Regression analysis, univariate and multivariate analyses between variables will be built for outcome variables to identify independent predictors. Variables such as age, sex, health facility, beliefs, education, economic status, employment status, religious status, disclosure, and months on ART will be considered as predictor variables or independent variables.

Materials and methods: Phase III

Objective 3: Understand adherence in first-line and second-line ART patients who are virologically suppressed and those who are not virologically suppressed in selected urban and rural communities.

Study design

The study will employ a qualitative study design approach. Active patients from phase I and II (in both urban and rural settings) will be invited to participate in the in-depth interviews (IDIs) to explore factors including (but not limited to) treatment history, current use of ART, treatment regimen, financial/economic factors, risk behaviours (substance use), psychosocial characteristics

cultural beliefs, spirituality and), relationship related factors (treatment support), community level factors (societal norms, stigma, discrimination, disclosure), and policy level factors (understanding/awareness of HIV/ART policies and treatment guidelines).

Study setting

This study will be conducted in seven health facilities in the city of Johannesburg region F in Gauteng Province and one in Limpopo Province (Ndlovu Medical Centre).

The seven health facilities in the city of Johannesburg include:

1. Primary Health Care: Jeppe Clinic, Malvern Clinic, Rosettenville Clinic, Yeoville Clinic
2. Community Health Centre: Hillbrow Community Health Center (HCHC)
3. Hospitals: Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and South Rand Hospital (SRH)

Sampling/Sample size

In this study, purposive sampling of patients currently taking ART will be employed to ensure maximum variation among the study sample. We will ensure a diverse sample by considering viral load status (suppressed and unsuppressed time on ART, age (18 years and older), sex (both males and females) and education. Sample size will depend on when saturation is reached; we anticipate that a maximum of 60 IDIs will be conducted across both study settings and viral load status groups (suppressed and unsuppressed). An anticipated number of study participants to recruit is 15 per viral load status group in each study setting (making a total of 30 participants in each study setting).

Data collection

Patients for this phase will be contacted using the contact information that they provided for their facility records or databases used in phase I and II. IDIs will be conducted following a semi-structured interview guide. The guide will comprise open-ended questions covering treatment history, current use of ART and multilevel factors derived from the socio-ecological framework. This will include individual level factors including treatment related factors (ART regimen, use of non-ART medication), financial and economic factors risk behaviours (substance use), psychosocial factors (cultural beliefs, spirituality), interpersonal-level factors (relationship between patients and treatment supporters or caregivers, such as intimate partners, family members, friends and health care workers), community level factors (social norms regarding HIV and ART, HIV-related stigma and discrimination, HIV-status disclosure), health-system factors (access to HIV and ART services including adherence counselling), and policy level factors (HIV testing and treatment guidelines and policies). Additional probes will be included for each question to promote sharing of detailed information regarding their perspectives and experiences, and to ensure clarification if required (see S1 Appendix study codebook and S2 Appendix interview

guide). All IDIs will be audio recorded and transcribed verbatim. Transcripts will be translated into English.

Deductive themes: Deductive themes may include treatment history, current use of ART, treatment regimen, financial/economic factors, risk behaviors (substance use), psychosocial characteristics cultural beliefs, spirituality and), relationship related factors (treatment support), community level factors (societal norms, stigma, discrimination, disclosure), and policy level factors (awareness of HIV/ART policies and treatment guidelines).

Data analysis

Transcripts will be imported and analysed using NVIVO. Data coding will be undertaken using deductive (top down) and inductive approaches (bottom up) [54]. A deductive approach is driven by researchers' analytic interest in the study, reflecting the broad issues addressed in the interview guide. An inductive approach is used to identify the detailed themes related to the overarching issues that can be identified in the data [54]. Thematic analysis will be used, which is a method for identifying, analysing, and reporting patterns (themes) within data [54,55]. Transcripts will be read while noting similar topics that will be grouped into major topics or themes. Data will be analysed as transcripts become available shortly after interviews are conducted. This will ensure the early identification of emerging themes and assist in the identification of data saturation. Analysis of the IDIs will follow the phases of thematic analysis which are familiarization, generating initial codes, searching for themes, reviewing themes and interpretation [54]. Familiarization (getting grounded into the data collected), will be achieved by reading the transcripts and field notes repeatedly. During the process of generating codes, key emerging ideas and words from the familiarization phase will be recorded from which we will search, identify, and review themes, concepts, categories, and sub-categories. This will be done in keeping with socio-ecological framework, views and experiences that persist from the data. Finally, factors that influence adherence to ART will be identified and grouped into main categories. Analysis will be guided by the codebook which will be developed by the study team post familiarization with the data. There will be multiple independent coders to ensure the reliability of the coding.

Materials and methods: Phase IV

Objective 4: Assess and compare adherence intervention strategies for the chronic conditions of HIV, hypertension and DM which have been tested and implemented in sub-Saharan Africa (Title: Adherence strategies and interventions for selected chronic conditions in sub-Saharan Africa: a systematic review and meta-analysis) (see S4 Appendix Systematic review protocol).

Study design

This systematic review will be designed and reported according to the PRISMA [56] (see S5 Appendix PRISMA checklist), following the registered protocol (CRD42019127564) on the international prospective register of systematic reviews, Prospero [57] (see S4 Appendix Systematic review protocol). The study will use PICO criteria as the search strategy tool.

A systematic review on the impact of treatment adherence interventions in chronic conditions (HIV, hypertension, DM) in sub-Saharan Africa will be conducted to provide context to adherence in sub-Saharan Africa. In this region, HIV remains the leading cause of death more especially in the young and middle-aged adults. However, the burden of non-communicable diseases (NCDs), particularly DM and hypertension, has increased rapidly in recent years [58–60].

Study setting

All information from sub-Saharan Africa only will be included for the systematic review.

Sampling/Sample size

All interventions described as chronic conditions adherence interventions (HIV/ART, hypertension, DM). Inclusion in the systematic review will be dependent on the criteria set out in the systematic review protocol [57] and reported using the PRISMA reporting guidelines.

Data collection

A pre-defined data sheet will be developed for data extraction. The tool will include (but not be limited to): reference (author, title), year of publication, setting or location, sample size, intervention description, participants receiving adherence (in case of comparison) (see S1 Appendix study codebook). The form/tool will be tested before conducting the final searches. One reviewer will conduct all the data extraction while a second reviewer will be responsible for data quality assurance on the extraction and also conduct full text review of the included material.

We will search using several electronic databases. These will include PubMed/Medline, Web of Science, Google Scholar, Scopus, and CINAHL. If necessary, we will contact study authors and request more information on individual studies. Citations and bibliographies of records will be reviewed to identify additional relevant material.

The basic search terms included will be:

"Chronic conditions" OR *"hypertension"* OR *"high blood pressure"* OR *"blood pressure"* OR *"arterial hypertension"* OR *"mellitus diabetes type I"* OR *"mellitus diabetes type II"* OR *"Diabetes"* OR *"Sugar"* OR *"HIV"* OR *"Antiretroviral Therapy"* OR *"Antiretroviral Treatment"* OR *"ART"* OR *"ART Programs"* OR *"ART Programmes"* AND *"adherence"* OR *"compliance"* AND *"interventions"* OR

"strategies" OR *"odds ratio"* OR *"risk ratio"* OR *"evaluation"* OR *"impact"* OR *"effectiveness"* OR *"outcome"* AND *"sub-Saharan Africa"* OR *"sub Saharan Africa"* OR *"sub-Saharan African"* OR *"sub Saharan African"* OR *"Africa"* (Table 1).

The search terms will be adjusted to suit the database being searched. An inventory with the database searched, the corresponding search criteria used, the date when the searches were conducted, and the results will be maintained. A second reviewer will run the searches separately for comparison. The strength of the body of evidence (quality of evidence), the risk of bias and magnitude of effect will be rated and assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) [61,62].

Outcome: The primary outcome will be adherence to antiretroviral therapy, defined as the proportion of patients meeting the defined adherence criteria. The secondary outcome will be proportion of patients achieving viral suppression, as defined by the study. Outcome (and impact) measures will be reported in terms of changes in the prevalence or reduction in the relative risk. Should there be adequate statistical reporting, a meta-analysis will be considered [63].

Data analysis

All adherence interventions or strategies will be described, based on the type of intervention implemented and the setting. The different evaluations methods will then be described in detail by comparing the type of assessments and outcome measures (adherence to ART and viral load). If appropriate, outcome measures will be reported in terms of changes in the prevalence or reduction in the relative risk. Whenever necessary, we will calculate unadjusted risk ratios (RRs) and 95% confidence intervals (CIs) from data provided and present the outcome indicator results in forest plots. Furthermore, we will perform a sensitivity analysis to measure the robustness of our results to the choice of summary statistic and calculated unadjusted risk differences. We will apply a random- effects model to calculate summary RRs and 95% Cl. To test the robustness of the findings, we will re-run the analysis using a fixed effects model. Data will be coded and analysed used STATA version 15.1. Details for study criteria are presented in Table 1.

Table 1: Methodological aspect of the systematic review

Criteria for study inclusion	Components details
Population (P)	Patients with selected chronic conditions (HIV, hypertension, DM) in sub-Saharan Africa
Intervention (I)	All interventions listed/described as adherence interventions or strategies for the conditions of HIV, hypertension, DM
Comparisons (C)	Standard of care and other adherence interventions reported on in the review
Outcome (O)	The included studies should report any measurement of adherence to chronic conditions – primarily, effects on adherence behaviour and the changes in health outcomes. There is no preferred measurement for reporting; should there be adequate statistical reporting, a meta-analysis will be considered.
Setting	All studies from sub-Saharan Africa only will be considered for the review.
Language	There will be no language restrictions.
Date	There will be no date/time restrictions.
Publication status	All the documented studies will be considered and included for review. This includes peer reviewed (i.e., papers, manuscripts, and abstracts).
Method	The study will be designed and reported according to PRISMA. PICO will be used as a search strategy approach. This study will describe reported adherence programmes and strategies. There will be a focus on behaviour change techniques used or reported changes in process outcomes of adherence programmes and methods of implementation for HIV, hypertension and /or DM.
Search strategy and selection procedure	We will search using several electronic databases. These will include: PubMed/Medline, Scopus, CINAHL, Web of Science and Google Scholar.
Search terms	(chronic conditions OR hypertension OR high blood pressure OR blood pressure OR arterial hypertension OR mellitus diabetes type I OR mellitus diabetes type II OR Diabetes OR Sugar OR HIV OR Antiretroviral Therapy OR Antiretroviral Treatment OR ART OR ART Programs OR ART Programmes) AND (adherence OR compliance) AND (interventions OR strategies OR odds ratio OR risk ratio or evaluation OR impact OR effectiveness OR outcome) AND (sub-Saharan Africa OR sub Saharan Africa OR sub-Saharan African OR sub Saharan African OR Africa)

Data management/Data cleaning (phase I-IV)

Data quality scripts for phase I, II, IV will be written in STATA. Data quality checks for phases I, II, and IV (quantitative data) will be done through RedCap (a secure web platform for building and managing research databases). Since TIER.Net will be used as the primary data source for phase I data extraction in the city of Johannesburg region F, where there are data quality issues, the study team will liaise with the facility staff and developmental partners in the region to assist with data clean-up activities. Data quality issues with the ITREMA data (phase II) will be communicated to the ITREMA study quality assurance officer for rectifying. Data quality checks for phase III (qualitative data) will be done in Microsoft Word (before exporting data to NVIVO). All transcripts will be checked for completeness and accuracy against original interviews. Creditability of data analysis will be ensured through triangulation of data sources (i.e., original interviews, field notes, transcripts, medical record).

Data storage and access (phase I-IV)

Data will be captured and stored electronically, and password protected in the Microsoft Word, Microsoft Excel format and/or RedCap and will only be accessible to an investigator and supervisors only. RedCap access is restricted to only those users who are registered on the system. All data from RedCap, Microsoft Word, Microsoft Excel, STATA, and voice files will be stored in access restricted folders on the Ezintsha server which will only be accessible to an investigator and supervisors. Any paper versions of data will be discarded after use. Data storage and access measures will also comply with data storage and access requirements of the Utrecht University.

Ethical approvals and consent to participate

We obtained ethical clearance for all the phases of the study from the University of the Witwatersrand Human Research Ethics Committee (clearance certificate number: M190641). Departmental approval was granted by the Johannesburg Health District (DRC Ref: 2019-10- 005 and National Health Research Database reference number: GP_201910_031). Written consent for interviews will be obtained from all participants. All participants will be provided with written information about the research, and they will also be verbally informed that their participation is voluntary and that they may withdraw from participation at any time (see S3 Appendix Participant Information sheet). There are no risks or direct benefits for participating in the study. Participants may benefit by taking part in the study because many people find that it is useful to discuss their experiences, opinions and provide feedback. We believe that the information from this study will help the South African Department of Health better understand and strengthen the ART services provided to patients at large. All participants will be informed of these benefits. All information discussed during the interview will be kept strictly confidential; at no point will participants' personal details be disclosed. The consent forms will be kept separately from all other research

documents. Only the study team will have access to the information provided by the participants. All dissemination outputs will present de-identified and, where possible, aggregated data.

DISCUSSION

The overarching aim of this study is to contribute to knowledge that can provide guidance regarding the barriers and facilitators to adherence for first-line and second-line ART patients and different adherence strategies utilized. Using an integrated multilevel socio-ecological framework, this study will focus on determining the influence of the multiple factors that impact on adherence to ART. In line with socio-ecological frameworks [64,65] and propositions, the findings from this study will be discussed under four units of analysis: intrapersonal level, interpersonal level, community level and policy level factors.

Intrapersonal factors

The client knowledge, attitudes, experiences and perceptions coupled with analysis of the intrapersonal factors influencing adherence to ART play a fundamental role in maintaining adherence [35]. Intrapersonal level factors such as being age, sex, substance abuse, and comorbidities will be discussed, in line with the existing literature [66–69].

Interpersonal level factors

The trust and communication between patients on ART and treatment supporters is essential in improving and maintaining optimal adherence to treatment [25]. Some studies have reported treatment support as a predictor of adherence [38,70]. In this study, the interpersonal level factors consisting of relationships between patients and family members, friends, intimate partner(s) and healthcare providers will be discussed against previous studies to provide guidance on the role of treatment supporters in strengthening treatment adherence.

Community level factors

The findings concerning community level factors will consider the importance of patients understanding of social norms, cultural barriers and reduction of poverty, stigma and discrimination against people living with HIV and on ART [71]. Information on poverty, culture, HIV related stigma, and discrimination caused by misconceptions will be discussed in line with existing literature to provide a critical assessment on the role of community level factors on ART adherence.

Policy level factors

The policy-level factors address awareness and influence of public health policies, guidelines, and standards on patients [72,73]. The South African HIV programme has undergone several changes since its implementation in 2004 [74]. This study will evaluate patient understanding/ awareness

of ART adherence or HIV treatment related health policies, guidelines, and best practices that are followed by health providers when providing health services. Knowledge of ART medicines or regimens (names of ART drugs), definitions, and clinical functions of viral load (knowledge of threshold for virological failure and suppression) and CD4 cell count (understanding of high or low CD4 cell count) will be discussed as themes in assessing individual's awareness of existing HIV treatment policies and guidelines. Additionally, we will be able to provide recommendations on required changes at the policy level to improve treatment adherence.

Strengths and limitations

To our knowledge this will be the first study using a social ecological perspective and a convergent parallel mixed method design to report on combination ART in South Africa. Combining quantitative and qualitative data from public health settings, a controlled environment, the patient perspective and evidence from the region will enable us to make recommendations for a comprehensive, acceptable, and appropriate adherence strategy for the country. The study presents a few limitations. The study will be conducted in a total of eight health facilities (seven of over 120 health facilities in one South African metropolitan municipality (urban setting) and one facility in a rural setting). Therefore, findings may not be generalizable to other municipalities and districts in South Africa, or to other country settings. Furthermore, although there are efforts to ensure good quality of data by the South African Department of Health, supporting partners and research staff, secondary data are subject to quality issues, due to data inconsistencies and missing data. Other potential predictors of adherence, such as disclosure, stigma, and self-reported adherence, will be assessed through a standard questionnaire. This may lead to reporting bias (memory and social desirability biases). Policy-level factors might not probe for relevant factors due to how this study is designed (with it focus on the individual's awareness of health policies and guidelines which is insufficient to fully assess policy-level factors).

In conclusion, our study will demonstrate how an existing socio-ecological conceptual framework can be used as a tool to provide guidance regarding facilitators and barriers to ART adherence. By populating this framework through secondary data analysis, participant interviews of PLHIV who are taking ART and a systematic review comparing adherence intervention strategies for the chronic conditions, this mixed method study will provide evidence on factors affecting treatment adherence at different socio-ecological levels and guide context specific intervention strategies to improve ART adherence. We believe that the use of our study results to strengthen adherence intervention will subsequently improve health outcomes and decrease the number of patients switching to complex treatment such as second-line and third-line regimens.

DISSEMINATION

Findings from this research will be submitted for doctoral degree purposes (by thesis). Peer reviewed publications and scientific conference presentations will be developed. Results of the research will be shared with the research participants, donors, and health facilities.

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Supplementary material 1: Codebook for all study phases

Phase I codebook: Secondary data analysis of a large cohort of patients on ART (from TIER.Net database)

Variables (from TIER.Net)	Description and codes
Patient unique number	Unique identity of a patient. The unique number vary by facilities and may also assist in picking duplicates
Facility	Name of a corresponding facility
Name	Name of the client/patient
Surname	Surname of the client/patient
Date Of Birth	The date of birth of the client/patient
Gender	Male of Female
Age At Pre-ART	This is applicable to patients who attended pre-Art prior to ART initiation and may be seen in older patients (before Universal Test and Treat)
Age At ART Start	This reflects age of the patient when started ART or restarted ART in case of defaulters or LTFU
Current Age	Refers to age of the patient at present (18 years and older)
First Visit Date	The first date the patient was seen in the facility (This date may be the same date as the diagnosis date)
HIV Diagnosis Date	Date the patient was confirmed as HIV positive
ART Start Date	Date of the patient's first ever experience with triple therapy (date when patient was started on ART for the first time ever) or re-initiated in case of Exp patients
Baseline CD4	First ever CD4 count done after HIV positive diagnosis (sometimes before starting the patient on ART). Before 2016, CD4 count was done after HIV positive status to assess patient's ART eligibility
Regimen At Baseline	First ever regimen issued to the patient when initiated on ART for the first time or when restated on ART (in case of defaulters or LTFU)
Method into ART	Patient has started ART at one facility and has now transferred to another facility

Method Into ART Location	For Transferred/Moved-In patients, facility/location where the patients come from (referring facility)
Transferred/Moved In Date	If client is a Transferred/Moved-in, Date when the client was transferred in the current clinic
Outcome	"Outcome" reflects active or inactive status of patients (whether the patient is still attending ART services in the facility or not). For active patients, this variable will be blank (however few blanks may also reflects unconfirmed lost to follow-up and this should be verified against Last ART visit date of the patient. In active patients will be coded as either Lost-to-follow up (LTFU), Transferred/Moved out and died.
Outcome Date	For inactive patients (LTFU, Transferred/Moved Out, Died), outcome date reflects date outcome was confirmed. For LTFU and Transferred/Moved Out-it reflects the last time the patient was at the facility
Prior ART	Reflects whether patient has ever taken ART before ART start date. Options listed as NO ART EXP (naïve), PMTCT, Prior ART > 30 days (EXPERIENCE).
Last ART Visit Code	Regimen that was given/issued to the patient at a last visit
Last ART Visit Date	The last visit date when the patient was seen in the facility. It is the date when the Last ART visit code was provided
Last ART CD4 Count	The last or latest CD4 count/result captured on TIER.Net. It is important to highlight that this depends on capturing and data quality i.e. blood results capturing into TIER.Net
Last ART CD4 Date	The date of the Last CD4 Count captured on TIER.Net
Last ART Next Appointment Date	This refers to the next ART appointment given to the patient at last ART visit. This date assists in ensuring that LTFU is calculated accurately
TB Rx Started	Did the client start on TB treatment (Yes,No, Not Sure). This is not at
Last ART VL Count	The last or latest Viral Load result captured on TIER.Net. It is important to highlight that this depends on capturing and data quality i.e. blood results capturing into TIER.Net
Last ART VL Date	The date of the Last Viral Load results captured on TIER.Net.
Second-Line Start Date	Second-Line Start Date. This is the date a patient was switched from first-line to a second-line regimen
Last ART Cell Code	Refers to the last regimen issued to the patient or last regimen that was expected to be issued to the patient. This includes the expected visits or appointments where the patients were unable to attend the clinic ("Did Not Attend").

Last ART Cell Date	Refers to the date of the Last ART Cell Code. With the description of a Last ART Cell Code, this might therefore be a future date when looked at against Last ART Visit Date
Last ART Prescription Code	Refers to regimen prescribed to the patient at a last ART visit. Sometimes this is similar to Last ART Visit Code
Last ART Prescription Date	This reflects the date of the last prescription provided to the patient. This may be similar to Last ART Visit Date
TB Status At Last Visit	Reflects TB screening and diagnosis at last visit. This includes the following options No Symptoms, Symptoms-With Sputum, Symptoms-No Sputum, On TB Treatment at this facility, On TB treatment at another facility, Not Screened, Screening Status Unknown
Pregnant on ART Start	Was the client/patient pregnant when starting ART
Pap Smear	Reflects whether pap smear was done to the patient (female)
Pap Smear Date	Reflects pap smear test date if pap smear was done
Last Sub Clinic	Name of the last Sub Clinic. This includes adherence clubs which mostly second-line patients will not be allocated to and in case this is captured, data quality may be required
Health Provider At ART Start	Name of the health provider who initiated/started the patient on ART
Pregnancy Status At Last Visit	Refers to pregnancy status in female patients at a last visit (listed as Yes, No or Not Sure). Screening for pregnancy is done at all visits unless the patient is pregnant
ART Restart Date After LTFU	In case the patient defaulted or was declared a LTFU, a date the patient was restarted on ART
Duration On ART (Months)	A period the patient has been on ART since first initiation or re-initiation (for experienced patients)

Phase II codebook: Secondary data analysis for the cohort from the ITREMA clinical trial

Question	Code	Numeric or textual	0	1	2	3	4	5	6	7	8	9
id	entry_no	1-600										
part_id	participant_no	ITREMA001-ITREMA600										
q4	employment		_	y_empl	y_self	n_unempl	n_stud	n_ret	n_dis	n_oth	ref	dk
q5	personal_pay	0-100000										
q6a	hh_in_salaries	0-100000										
q6b	hh_in_business	0-100000										
q6c	hh_in_remittance	0-100000										
q6d	hh_in_pension	0-100000										
q6e	hh_in_grants	0-100000										
q6f	hh_in_other	0-100000										
q7a	grant_age		no	yes								
q7b	grant_disability		no	yes								
q7c	grant_child_sup		no	yes								
q7d	grant_care		no	yes								
q7e	grant_foster_child		no	yes								
q7f	grant_veteran		no	yes								
q7g	grant_in_aid		no	yes								
q7h	grant_social		no	yes								
q7i	grant_refused		no	yes								
q7j	NA	NA	NA	NA	NA	NA	NA					
q8a	rela_status		_	married	life_part	half	single	divorced	widowed	multiple	other	
q8b	rela_start	date										
q8c	rela_other	text										
q9	people_under_roof	0-20										
q10a	hh_partner	0-5										

q10b	hh_child_bio	0-20										
q10c	hh_child_other	0-20										
q10d	hh_parent	0-2										
q10e	hh_in law	0-2										
q10f	hh_sibling	0-20										
q10g	hh_grandparent	0-8										
q10h	hh_other_fam	0-20										
q10i	hh_non_relative	0-20										
q10j	hh_refused		no	yes								
q10k	hh_dk		no	yes								
q11	no_money_food		_	yes	no	dk						
q12	nf_recent		n/a	yes	no	dk						
q13	nf_how_often		n/a	yes	no	dk						
q14	nf_hungry		n/a	yes	no	dk						
q15a	nf_jan		no_n/a	yes								
q15b	nf_feb		no_n/a	yes								
q15c	nf_mar		no_n/a	yes								
q15d	nf_apr		no_n/a	yes								
q15e	nf_may		no_n/a	yes								
q15f	nf_jun		no_n/a	yes								
q15g	nf_jul		no_n/a	yes								
q15h	nf_aug		no_n/a	yes								
q15i	nf_sep		no_n/a	yes								
q15j	nf_oct		no_n/a	yes								
q15k	nf_nov		no_n/a	yes								
q15l	nf_dec		no_n/a	yes								
q15m	nf_dk		no_n/a	yes								
q16	ARV_ability		_	compl_unsure	unsure	sure	compl_sure					

q17	ARV_positive_effect		_	compl_unsure	unsure	sure	compl_sure					
q18	ARV_resistance		_	compl_unsure	unsure	sure	compl_sure					
q19	ss_satisfaction		_	v_dissat	sw_dissat	sw_satis	v_satis					
q20	ss_remember_medication		_	not_at_all	somewhat	a_little	a_lot	n/a				
q21	md_away		_	never	rarely	sometimes	often	n/a				
q22	md_busy		_	never	rarely	sometimes	often	n/a				
q23	md_forgot		_	never	rarely	sometimes	often	n/a				
q24	md_too_many		_	never	rarely	sometimes	often	n/a				
q25	md_side_effect		_	never	rarely	sometimes	often	n/a				
q26	md_privacy		_	never	rarely	sometimes	often	n/a				
q27	md_routine		_	never	rarely	sometimes	often	n/a				
q28	md_harmful		_	never	rarely	sometimes	often	n/a				
q29	md_asleep		_	never	rarely	sometimes	often	n/a				
q30	md_sick		_	never	rarely	sometimes	often	n/a				
q31	md_depression		_	never	rarely	sometimes	often	n/a				
q32	md_specific_time		_	never	rarely	sometimes	often	n/a				
q33	md_empty		_	never	rarely	sometimes	often	n/a				
q34	md_felt_good		_	never	rarely	sometimes	often	n/a				
q35	often_on_time		_	all_time	most_time	rarely	never	n/a				
q36	md_days_week		_	every_day	4_to_6	2_to_4	once	less_once	never	n/a		
q37	md_last time		_	past_week	1_to_2w	2_to_4w	1_to_3m	more_3m	never	n/a		
q38	hh_supp_work		_	no_sup	little_sup	fair_sup	lot_sup					
q39	hh_supp_worries		_	no_sup	little_sup	fair_sup	lot_sup					
q40	hh_supp_leisure		_	no_sup	little_sup	fair_sup	lot_sup					
q41	hh_supp_practical		_	no_sup	little_sup	fair_sup	lot_sup					
q42	hh_supp_personal		_	no_sup	little_sup	fair_sup	lot_sup					
q43	non_hh_supp_work		_	no_sup	little_sup	fair_sup	lot_sup					
q44	non_hh_supp_worries		_	no_sup	little_sup	fair_sup	lot_sup					

q45	non_hh_supp_leisure		_	no_sup	little_sup	fair_sup	lot_sup					
q46	non_hh_supp_practical		_	no_sup	little_sup	fair_sup	lot_sup					
q47	non_hh_supp_personal		_	no_sup	little_sup	fair_sup	lot_sup					
q48	stress_get_away		_	never	rarely	sometimes	v_often	always				
q49	stress_solve_problem		_	never	rarely	sometimes	v_often	always				
q50	stress_blame_situation		_	never	rarely	sometimes	v_often	always				
q51	stress_treat_food		_	never	rarely	sometimes	v_often	always				
q52	stress_anxious		_	never	rarely	sometimes	v_often	always				
q53	stress_similar_problem		_	never	rarely	sometimes	v_often	always				
q54	stress_visit_friend		_	never	rarely	sometimes	v_often	always				
q55	stress_determine_action		_	never	rarely	sometimes	v_often	always				
q56	stress_buy_me		_	never	rarely	sometimes	v_often	always				
q57	stress_blame_emotional		_	never	rarely	sometimes	v_often	always				
q58	stress_work_understand		_	never	rarely	sometimes	v_often	always				
q59	stress_upset		_	never	rarely	sometimes	v_often	always				
q60	stress_corrective_action		_	never	rarely	sometimes	v_often	always				
q61	stress_blame_knowing		_	never	rarely	sometimes	v_often	always				
q62	stress_special_person		_	never	rarely	sometimes	v_often	always				
q63	stress_think_learn		_	never	rarely	sometimes	v_often	always				
q64	stress_wish_change		_	never	rarely	sometimes	v_often	always				
q65	stress_go_food		_	never	rarely	sometimes	v_often	always				
q66	stress_analyze_react		_	never	rarely	sometimes	v_often	always				
q67	stress_inadequacies		_	never	rarely	sometimes	v_often	always				
q68	stress_phone_friend		_	never	rarely	sometimes	v_often	always				
q69	hcw_depend		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q70	hcw_understand		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q71	hcw_distrust		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q72	hcw_joint_effort		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			

q73	hcw_similar_ideas		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q74	hcw_respect		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q75	hcw_like		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q76	hcw_relationship		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q77	hcw_experienced		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q78	hcw_likes_me		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q79	hcw_distant		_	stro_disagr	disagr	sli_disagr	sli_agree	agree	stro_agree			
q80	CD4_what	text										
q81	ARV_CD4		_	up	down							
q82	VL_what	text										
q83	ARV_VL		_	up	down							
q84	current_med_HIV	text										
q85	take_ARV_bad		_	agree	unsure	disagr						
q86	take_ARV_tired		_	agree	unsure	disagr						
q87	take_ARV_down		_	agree	unsure	disagr						
q88	take_ARV_taste		_	agree	unsure	disagr						
q89	take_ARV_good		_	agree	unsure	disagr						
q90	mental_interest		_	not_at_all	sev_days	half_days	every_day	refuse				
q91	mental_depressed		_	not_at_all	sev_days	half_days	every_day	refuse				
q92	mental_sleep		_	not_at_all	sev_days	half_days	every_day	refuse				
q93	mental_tired		_	not_at_all	sev_days	half_days	every_day	refuse				
q94	mental_appetite		_	not_at_all	sev_days	half_days	every_day	refuse				
q95	mental_me_failure		_	not_at_all	sev_days	half_days	every_day	refuse				
q96	mental_concentration		_	not_at_all	sev_days	half_days	every_day	refuse				
q97	mental_slow_restless		_	not_at_all	sev_days	half_days	every_day	refuse				
q98	mental_suicide		_	not_at_all	sev_days	half_days	every_day	refuse				
q99	stigma_dirty		_	stro_disagr	disagr	agree	stro_agree					
q100	stigma_cursed		_	stro_disagr	disagr	agree	stro_agree					

q101	stigma_trust		_	stro_disagr	disagr	agree	stro_agree					
q102	stigma_similar		_	stro_disagr	disagr	agree	stro_agree					
q103	stigma_ashamed		_	stro_disagr	disagr	agree	stro_agree					
q104	stigma_not_guilty		_	stro_disagr	disagr	agree	stro_agree					
q105	stigma_weak		_	stro_disagr	disagr	agree	stro_agree					
q106	stigma_safe_children		_	stro_disagr	disagr	agree	stro_agree					
q107	stigma_restrictions		_	stro_disagr	disagr	agree	stro_agree					
q108	stigma_punishment		_	stro_disagr	disagr	agree	stro_agree					
q109	stigma_isolated		_	stro_disagr	disagr	agree	stro_agree					
q110	stigma_allow_work		_	stro_disagr	disagr	agree	stro_agree					
q111	stigma_friendship		_	stro_disagr	disagr	agree	stro_agree					
q112	stigma_family_care		_	yes	no							
q113	stigma_disclosure_family		_	yes	no							
q114	no_sex_partner_12m	0-50										
q115	no_sex_partner_1m	0-10										
q116a	initial_part1	text										
q116b	initial_part2	text										
q116c	initial_part3	text										
q116d	initial_part4	text										
q116e	initial_part5	text										
q116f	initial_part6	text										
q116g	initial_part7	text										
q116h	initial_part8	text										
q117a	age_part1	0-100										
q117b	age_part2	0-100										
q117c	age_part3	0-100										
q117d	age_part4	0-100										
q117e	age_part5	0-100										

q117f	age_part6	0-100										
q117g	age_part7	0-100										
q117h	age_part8	0-100										
q118a	sex_part1	0-62										
q118b	sex_part2	0-62										
q118c	sex_part3	0-62										
q118d	sex_part4	0-62										
q118e	sex_part5	0-62										
q118f	sex_part6	0-62										
q118g	sex_part7	0-62										
q118h	sex_part8	0-62										
q119a_y	years_part1	0-90										
q119b_y	years_part2	0-90										
q119c_y	years_part3	0-90										
q119d_y	years_part4	0-90										
q119e_y	years_part5	0-90										
q119f_y	years_part6	0-90										
q119g_y	years_part7	0-90										
q119h_y	years_part8	0-90										
q119a_m	months_part1	0-12										
q119b_m	months_part2	0-12										
q119c_m	months_part3	0-12										
q119d_m	months_part4	0-12										
q119e_m	months_part5	0-12										
q119f_m	months_part6	0-12										
q119g_m	months_part7	0-12										
q119h_m	months_part8	0-12										
q119a_d	days_part1	0-31										

q119b_d	days_part2	0-31										
q119c_d	days_part3	0-31										
q119d_d	days_part4	0-31										
q119e_d	days_part5	0-31										
q119f_d	days_part6	0-31										
q119g_d	days_part7	0-31										
q119h_d	days_part8	0-31										
q120a	condom_part1		_	always	half_time	rarely	never					
q120b	condom_part2		_	always	half_time	rarely	never					
q120c	condom_part3		_	always	half_time	rarely	never					
q120d	condom_part4		_	always	half_time	rarely	never					
q120e	condom_part5		_	always	half_time	rarely	never					
q120f	condom_part6		_	always	half_time	rarely	never					
q120g	condom_part7		_	always	half_time	rarely	never					
q120h	condom_part8		_	always	half_time	rarely	never					
q121	sex_money		_	never	sometimes	often	always					
q122	alcohol		_	never	less_m	monthly	weekly	daily				
q123	alcohol_six		_	never	less_m	monthly	weekly	daily				
q124	alcohol_memory		_	never	less_m	monthly	weekly	daily				
q125a	use_dagga		no	yes								
q125b	use_benzene		no	yes								
q125c	use_mandrax		no	yes								
q125d	use_iv		no	yes								
q125e	use_nyaope		no	yes								
q125f	use_glue		no	yes								
q125g	use_other		no	yes								

Phase III codebook: Participant's understanding of adherence (and their recommendations to improve adherence to medication) (in-depth interviews)

Themes	Guide	Codes
Participant's life context	Information about participant's time on ART and mentioning their age, gender, ethnicity and how long you have been on medication. Investigation on their knowledge about ART	Participant's Life context Age Gender Ethnicity and Duration on ART Knowledge about ART
Treatment history	Information about the time the particpant was diagnosed with HIV, when they started on treatment, (include the time it took to start treatment). Discussing the time treatment was interrupted or stopped and reasons for interruptions	Treatment history HIV diagnosis ART start information Treatment interruptions Adherence counselling Reasons for starting treatment, Duration it took to start ART (and reasons for taking longer/shorter)
	If ever stopped ART for a month or longer, reasons for restarting ARVs again?	Restarting ART, Health complications, Self-motivation, Adherence counselling
		Support from relative/family member/partner/friends

Current use of ART	Experiences on taking ART medication. What makes participants take their medication. Also discussing current challenges with taking ART correctly or as prescribed	Factors associated with ART adherence (facilitators and barriers to ART adherence). Treatment taking behaviour, Motivation to take treatment Current challenges or difficulties with taking ART, Effects of comorbidities Distance to health facilities Education on ART adherence
Individual level factors (intrapersonal)	Discussing on the feeling of taking ART/ARVs.	Regimen related factors Effect of size of the pill(s) Pill burden Dosages Frequencies Side effects.
	Discussing the participant's views on substance use (alcohol and drugs) while taking ART or replacing treatment with other non-ART medications or stopping treatment completely? Discusing the views on the role of cultural beliefs and spirituality towards ART adherence?	Substance use (alcohol and drugs) Non-ART medication Cultural beliefs and spirituality Effects of substance and drug abuse (towards ART adherence) and using non-ART medications, effects Influence of religion and cultural beliefs on adherence (both positive and negative)
	Discussing the role of having employment, financial means or reliable transport to a health facility affects adherence to treatment	Financial related/economic factors Effects of lack of financial support Lack of employment Poverty
		Lack of transportation to a health facility.

Relationships level factors (interpersonal)	Discussing the role of treatment supporters? Or people who help take treatment better? It could be family members, partner, friend or health care worker?	Treatment support, Role of treatment supporters (family members, partner(s), relatives, friends and health care workers. Trust Confidentiality Communication
Community-level factors	Discussing how the community/society feel about people with HIV or on ART? The impact of discrimination and stigma towards ART patients? Discussig issues around disclosure of HIV status and taking ART Discussing veiws about ART services available within the health facility (including adherence services)?	Societal norms/stigma Discrimination and disclosure, Societal perceptions and views Social norms Poverty, Disclosure, Access and availability of health services within health facilities.
Policy level factors (Macrolevel factors or healthcare policy factors)	Discussing views on the role of ART policies and guidelines towards ART adherence?	Guidelines and policies, Participants have knowledge and an understanding of the role of policies and guidelines Guidelines play a role towards ART adherence
Treatment taking reminders	Discussing treatment taking reminders if any	Treatment taking reminders, treatment storage. Reasons for using the specific reminders and storage.
Recommendations for adherence strategies	Discussing what participants think should be done to improve adherence of patients on ART?	Recommendations for adherence strategies,
Closing	Discussing any other issues a participant would like to raise regarding ART?	

Phase IV codebook: Systematic review data collection (article extraction form)

	#	Variable/Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: Article extraction form				
	1	record_id	Article number	text
	2	authors	Authors	text
	3	title	Title	text
	4	year_published	Year article published	text
	5	abstract	Abstract	notes
	6	journal	Journal	text
	7	objectives	Objectives	text
	8	population	Study population	text
	9	Study design	Study design	text
	10	sample_size	Sample size	text
	11	adherence_strategy1	Adherence strategy 1	text
	12	adherence_strategy2	Adherence strategy 2	text
	13	adherence_strategy3	Adherence strategy 3	text
	14	adherence_strategy4	Adherence strategy 4	text
	15	adherence_strategy5	Adherence strategy 5	text
	16	comparison_s	Comparison(s)	text
	17	outcome	Outcome	text
	18	comments	Comments	notes

Supplementary material 2: Semi-structured Interview guide

Title of Study: Strengthening understanding of effective adherence strategies for first-line and second-line antiretroviral therapy (ART) in selected rural and urban communities in South Africa

INSTRUCTIONS

1. This interview is intended to be an informal conversation to collect information regarding factors (facilitators and barriers) associated with adherence on first-line and second-line ART regimen and strategies to improve adherence to treatment 2. Each interview must be audio recorded ONLY after the informed and recording consent form have been signed.
3. There are two levels of questions:
    a. Main questions: the questions that the investigators want to get answers to b. Probes: to assist the moderator to get greater clarity on certain issues and more information about the main question

If the interviewer is different from the person consenting:

Hello, my name is _____ and I am an employee at Ezintsha, a subdivision of Wits Reproductive Health and HIV Institute (Wits RHI). I would like to invite you to participate in an interview to understand factors (facilitators and barriers) associated with adherence on first-line and second-line regimen and strategies to improve adherence to treatment.

Please note that I simply want to hear your views, and there is no right or wrong answer; everything you say is important. Please feel free to speak openly and use any language or words that best describe your experiences and views. Your real name will not be written anywhere, which means that no one will know it was you who said something. I will like to record the interview using an audio recorder to help me remember all the information from our conversation. We will transcribe (write out) what you have said. The voice files and notes will be kept private and safe. The discussion will take about 45 – 60 minutes.

Date of interview (DD/MM/YYYY): _____ Client initials: _____ Clinic name: _____

Tier or study unique #: _____ Viral load status (VLS or VLF) _____

Last viral load count (number, check the patient file or TIER.Net): _____

Guide #_____

Themes	Sub-themes	Main questions *Probes* *[Use probes when you need to clarify the main question or to obtain more information from the participant]*	Notes
Participant's life context	Life context	Tell me a bit about yourself (not mentioning your name but maybe your age, gender, ethnicity and how long you have been on medication/ART)? What do you understand and know about ART? *Probe* *Probe to allow sufficient introduction from participants that will include socio-demographic information (gender, age and ethnicity) and allow participants to be free and expressive. Probe whether participants know how long they have been on ART.* *Probe on whether participants know why they take ART.*	Life context
Treatment history	HIV diagnosis, when started ART, treatment interruptions	Please tell me about the time you were diagnosed with HIV, when you were started on treatment, (include the time it took you to start treatment) Please tell me about the time you interrupted or stopped ART (if ever) for over one month. What	Treatment history

		made you stop taking your treatment or interrupt treatment? ***Probe*** *Probe from responses provided by participants. Probe on how participants felt after diagnosis, whether adherence counselling was provided after diagnosis, discussed starting treatment with the health care worker, reasons for starting treatment, duration it took to start ART (and reasons for taking longer/shorter),* *Probe if participants have ever interrupted and reasons for treatment interruption.*	
	Restarting ART	If ever stopped ART for a month or longer, why did you decide to restart ARVs again? *(Skip this question if participant has never stopped treatment)* ***Probe*** *Probe from responses provided by participants. Probe on reasons for restarting ART (health complications, self-motivation, adherence counselling, support from relative/family member/partner/friends)*	Restarting ART
Current use of ART	Facilitators and barriers to ART adherence	Tell me about your experience taking your medication. What makes you take your medication?	Factors associated with ART adherence

		Tell me about your current challenges with taking ART correctly or as prescribed? ***Probe*** *Probe from responses provided by participants. Probe about what affects their treatment taking behaviour, motivation to take treatment, current challenges or difficulties with taking ART* *Probe about effects of comorbidities, distance to health facilities, education on ART adherence (leading to other individual factors below).* *NOTE: This section efficiently introduces socioecological levels (below) as participants are likely to mention related factors here.*	
Individual level factors (intrapersonal)	Regimen related factors	Tell me what it is like to take ART/ARVs? How do you feel about the drugs you are taking? ***Probe*** *Probe from responses provided by participants. Probe about effect of size of the pill(s), pill burden, dosages, frequencies and side effects.*	Regimen related factors
	Effects of substance use (alcohol and drugs), non-ART medication, cultural beliefs and spirituality towards adherence to ART	What are your views on substance use (alcohol and drugs) while taking ART or replacing treatment with other non-ART medications or stopping treatment completely? What are your views on the role of cultural beliefs and spirituality towards ART adherence?	substance use (alcohol and drugs), nonART medication, cultural beliefs and spirituality

		Probe *Probe from responses provided by participants. Probe about the effects of substance and drug abuse (towards ART adherence) and using nonART medications (could be in addition to ART or replacing ART with non-ART medications). Probe on the effects and influence of religion and cultural beliefs on adherence (both positive and negative).*	
	Financial related/economic factors	How do you think having employment, financial means or reliable transport to a health facility affects adherence to treatment? *Probe* *Probe from responses provided by participants. Probe about the effects of lack of financial support, lack of employment, poverty, lack of transportation to a health facility towards ART adherence.*	Financial related/economic factors
Relationships level factors (interpersonal)	Treatment support	Tell me about what you think of treatment supporters? Or people who help you take treatment better? It could be a family member, partner, friend or health care worker? Probe *Probe from responses provided by participants. Probe on participants' views about the role of treatment supporters towards ART adherence.* *This includes family members, partner(s),*	Treatment support

		relatives, friends and health care workers. Also probe using the following relationship factors: trust, confidentiality and communication. Probe on the participant's relationship with health care workers at the clinic? Does it have effect on adherence to medication?	
Community-level factors	Societal norms/stigma, discrimination and disclosure	How do you think the community/society feel about people with HIV or on ART? What do you think is the impact of discrimination and stigma towards ART patients? How do you feel about talking to other people about your HIV status (disclosure) or that you are taking ART medication? How do you feel about ART services available within the health facility (including adherence services)? ***Probe*** *Probe on how community level factors affect ART adherence (probe from participant responses).* *Probe about the societal perceptions and views on people with HIV/AIDS (or people taking ART), with more focus on social norms, poverty, disclosure, HIV related discrimination and stigma, and access and availability of health services within health facilities.*	Societal norms/stigma, discrimination and disclosure

Policy level factors (Macro-level factors or healthcare policy factors)	Guidelines and policies	What are your views on the role of ART policies and guidelines towards ART adherence? ***Probe*** *Probe from participant responses.* *Probe whether participants have knowledge and an understanding of the role of policies and guidelines and participants views on whether policies and guidelines play a role towards ART adherence*	Guidelines and policies
Treatment taking reminders		Talk to me about what you use as a reminder to take your medication? Why do you use it? ***Probe*** *Probe from participant responses.* *Probe about what makes participants remember to take tablets, treatment storage, and reasons for using the specific reminders and storage.*	Treatment taking reminders
Recommendations for adherence strategies		In your opinion, what do you think should be done to improve adherence of patients on ART? ***Probe*** *Probe from participant responses. Probe about any adherence strategies or treatment support that participants can recommend in order to take medication correctly. It could be a strategy or treatment support that is currently offered or would like to see offered.*	Recommendations for adherence strategies

Closing	We have come to the end of our interview, do you have any issues that you would like to raise regarding ART? Do you have any additional comments on how ART adherence or treatment taking behaviour can be improved?	

Signature of interviewer _____ Date _____

Supplementary material 3: Participant information sheet

Title of Study: Strengthening understanding of effective adherence strategies for first-line and second-line antiretroviral therapy (ART) in selected rural and urban communities in South Africa

Principal Investigator: Siphamandla Gumede **Institution: Ezintsha/School of Clinical Medicine, Wits University/Utrecht University/Department of Interdisciplinary Social Science**

Participant Information Sheet

Introduction and purpose of the study:

Hello, my name is _____and I am a PhD student at the University of the Witwatersrand, South Africa and Utrecht University, Netherlands. I am also an employee at Ezintsha, a subdivision of Wits Reproductive Health and HIV Institute (Wits RHI). I am recruiting 60 people to participate in a study to understand effective adherence strategies for first-line and second-line antiretroviral therapy (ART) in eight of the healthcare facilities in the City of Johannesburg Region F and Ndlovu Medical Centre, Elandsdoorn, Limpopo. Because you are currently taking first-line or second-line regimen in one of these facilities, I would like to invite you to participate in an interview, to be held at a mutually agreed upon venue, date and time. The information gathered from this interview will help to understand factors (facilitators and barriers) associated with adherence on first-line and second-line regimen.

This information form is to help you decide if you would like to give your permission to participate. You should fully understand what is involved before you decide to take part in this study. If you have any questions, do not hesitate to ask me. You should not agree to take part unless you are satisfied about all the procedures involved. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. Should you require it you can have a copy of this form to keep.

Procedure:

During the interview, we will cover two types of questions – ones in which I will give you alternatives and you chose one and other questions in which you can answer with your own answer. The interview should take 45- 60 minutes. I would also like to record the interview using an audio recorder to help me remember all the information from our conversation. This will only be done however with your consent. We will transcribe (write out) what you have said. Our discussion will be confidential, and your name will not be recorded with the tape recording. There will be no way of linking what you say in this interview to who you are. Only the staff from the research study, from Ezintsha will see this information. The audio recording will be retained for a minimum of two and a maximum of six years. You may still participate in the interview should you wish not to be audio recorded. In this case, I will administer the questionnaire and write down notes as I ask you the questions.

Consent:

Your participation in this interview process is completely voluntary (this means you, and only you, can choose whether you would like to join this study). You may refuse to answer any specific question if you feel uncomfortable with that question. You do not have to give me a reason for refusing to answer specific questions. You can also decide to stop participating at any time. If you decide that you don't want to be part of this study, there will be no negative consequences for you and it will have no impact on your accessing health care services/working within this clinic or anywhere else. There are no right or wrong answers to any of the questions. I only want to know about your experiences, views, comments, opinions and ideas.

Confidentiality:
All information discussed during the interview will be kept strictly confidential; at no point will your personal details be disclosed.
Your consent form will be kept separately from all other research documents. Only I, and co-investigators will have access (through Ezintsha) to the information you have provided. During data analyse, it will all be put together without any names so that when it is reported, no person who participated in the interviews can be identified. This study protocol has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg.

Benefits:
We think that you will probably benefit by participating because many people find that it is useful to discuss their experiences, opinions and provide feedback. I believe that the information you provide will help Wits RHI and Department of Health better understand and strengthen the Anti-Retroviral Therapy services provided to patients at large.

Risks:
There are no known risks to participants

Cost:
There are no costs to you to participate in the study. If you do participate, you will be provided with R150.00 as reimbursement for your travel and time.

Rights of the Participant:
You may find it uncomfortable to express your personal opinions in front of an interviewer. We want you to feel comfortable so please let us know if you feel uncomfortable. You don't have to answer any questions that you don't want to discuss and you can leave the stop the interview at any time, even if it is just for a break.

Further information:
You may contact me, or my supervisor, at any time with any question you may have regarding this study – details below:

Principal Investigator: Mr Siphamandla Gumede
Tel: 011 358 5553
Email: sgumede@ezintsha.org/sgumede@cartafrica.org

Supervisor: Dr Samanta Lalla-Edward
Tel: 011 358 5404
Email: slalla-edward@ezintsha.org

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.
If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Prof Clement Penny, who may be contacted on telephone number 011 717 2301, or by email on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

October 2019

Participant Initials: ____

A. Approved by WITS HUMAN RESEARCH ETHICS COMMITTEE on _____

Supplementary material 4: Systematic review protocol

Title: Adherence strategies and interventions for selected chronic conditions in sub-Saharan Africa: a systematic review

Siphamandla B Gumede[1,2*]; John BF de Wit[2]; WD Francois Venter[1]; Samanta T Lalla-Edward[1]; Maaike Noorman[2]

1 Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
2 Department of Interdisciplinary Social Science, Faculty of Social and Behavioural Sciences, Utrecht University

Systematic review conducted by Siphamandla B Gumede

Reviewer/Guarantor 1: Samanta T Lalla-Edward (slalla-edward@ezintsha.org)

Reviewer/Guarantor 2: Willem Daniel Francois Venter (fventer@ezintsha.org) Reviewer/Guarantor 3: John BF de Wit (j.dewit@uu.nl)

Background

Adherence is widely defined as patient's ability to follow a treatment plan and take medications at prescribed times (1–3). Poor adherence to treatment is a limiting factor in the successful health outcomes of numerous health conditions, including HIV, hypertension and diabetes mellitus (DM) (4–6). Globally reports have indicated that up to 50% of treatment for chronic or long term conditions are not taken as recommended by health providers (7–9). In SubSaharan Africa, a wide range of barriers to adherence for chronic conditions have been reported, including adverse drug reactions, competing responsibilities, frequencies of treatment intake, tolerability, cost of treatment, food insecurity, stigma, lack of human health resources and social factors (10–12)

In the efforts to address adherence to treatment for the chronic conditions; behavioural and psychological factors, education, integrated care and patient self-management interventions have been explored (12–14). This includes behavioural rehabilitation provided by health providers to patients, integration of pyscho-social support within health programmes, and patient's knowledge about the medication and their overall satisfaction with the treatment (12,15,16). Other studies have recommended telephonic counselling and text messaging or reminders (mobile health), packaging/medication boxes, home visits, drug level monitoring, consistent clinical monitoring of patients (12,17–19). Studies focusing on ART adherence have further emphasized the importance of compliance with standard treatment guidelines (monitoring and reporting of health information (data) to promote appropriate medicine use (10,20–22).

Research question

What treatment adherence strategies and interventions for chronic conditions have been tested and implemented in sub-Saharan Africa?

Objective

To assess and compare adherence intervention strategies for the chronic conditions of HIV, DM and hypertension which have been tested and implemented in sub-Saharan Africa.

Inclusion criteria

a. Population: Patients with selected chronic conditions (HIV, hypertension, DM) in subSaharan Africa.
b. Intervention: All interventions listed/described as adherence interventions or strategies for the conditions of HIV, hypertension, DM.
c. Comparisons: Standard of care and other interventions reported on in the review

d. Outcome: The included studies should report any measurement of adherence to chronic conditions – primarily, effects on adherence behaviour and the changes in health outcomes. There is no preferred measurement for reporting; should there be adequate statistical reporting, a meta-analysis will be considered.
e. Setting: All information from sub-Saharan Africa only will be considered for the review.
f. Language: There will be no language restrictions.
g. Date: There will be no date/time restrictions.
h. Publication status: All the documented studies will be considered and included for review. This includes peer reviewed (i.e., papers, manuscripts, and abstracts).
i. Method: The study will be designed and reported according to PRISMA. PICO will be used as a search strategy approach. This study will describe reported adherence programmes and strategies. There will be a focus on behaviour change techniques used or reported changes in process outcomes of adherence programmes and methods of implementation for HIV, hypertension and /or DM.

Search strategy and selection procedure

We will search using several electronic databases. These will include PubMed/Medline, Web of Science, Google Scholar, Scopus, and CINAHL. If necessary, we will contact study authors and request more information on individual studies. Citations and bibliographies of records will be reviewed to identify additional relevant material.

The basic search terms included will be:

"Chronic conditions" OR *"hypertension"* OR *"high blood pressure"* OR *"blood pressure"* OR *"arterial hypertension"* OR *"mellitus diabetes type I"* OR *"mellitus diabetes type II"* OR
"Diabetes" OR *"Sugar"* OR *"HIV"* OR *"Antiretroviral Therapy"* OR *"Antiretroviral Treatment"* OR *"ART"* OR *"ART Programs"* OR *"ART Programmes"* AND *"adherence"*
OR *"compliance"* AND *"interventions"* OR *"strategies"* OR *"odds ratio"* OR *"risk ratio"*
OR *"evaluation"* OR *"impact"* OR *"effectiveness"* OR *"outcome"* AND *"sub-Saharan Africa"* OR *"sub Saharan Africa"* OR *"sub-Saharan African"* OR *"sub Saharan African"* OR *"Africa" (table 1).*

The search terms will be adjusted to suit the database being searched. An inventory with the database searched, the corresponding search criteria used, the date when the searches were conducted, and the results will be maintained. The principal investigator will do all the searches and the second reviewer will run the searches separately for comparison. The strength of the body of evidence (quality of evidence), the risk of bias and magnitude of effect will be rated and assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) (23,24).

Data collection and management

A pre-defined data sheet will be developed for data extraction. The tool will include (but not be limited to): reference (author, title), year of publication, setting or location, sample size, intervention description, participants receiving adherence (in case of comparison). The form will be piloted prior to be used for the final searches. The principal investigator will do all the data extraction. A second and third reviewers will conduct a quality control check on the extraction and assist with the full text review of the included material.

Data quality checks will be done through RedCap (a secure web platform for building and managing research databases).

Data storage

Data will be captured and stored electronically, and password protected in the Microsoft Excel format and/or RedCap and will only be accessible to an investigator and reviewers only. RedCap access is restricted to only those users who are registered on the system.

Analysis

All adherence interventions or strategies will be described, based on the type of intervention implemented and the setting. The different evaluations methods will then be described in detail by comparing the type of assessments and outcome

measures. If appropriate, outcome measures will be reported in terms of changes in the prevalence or reduction in the relative risk. Whenever necessary, we will calculate unadjusted risk ratios (RRs) and 95% confidence intervals (CIs) from data provided and present the outcome indicator results in forest plots. Furthermore, we will perform a sensitivity analysis to measure the robustness of our results to the choice of summary statistic and calculated unadjusted risk differences. We will apply a random- effects model to calculate summary RRs and 95% Cl. To test the robustness of the findings, we will re-run the analysis using a fixed effects model. Data will be coded and analysed used STATA version 15.1.

Publication

The corresponding author will produce the first draft manuscript which will be commented on by all co-authors. The systematic review will be submitted to a peer-reviewed journal.

Duration

The review is expected to take twelve months from protocol development to manuscript submission.

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Supplementary material 5: PRISMA-P checklist (page numbers aligned with the published paper presented in chapter 2)

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	18
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	18
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	26,27
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	2
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	2
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	2
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	2/protocol in prospero
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	10,18
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	21,22
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	19,20

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	20,22
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	22,23
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	19,20
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	19,20
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	21,22
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	21,22
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	20-22
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	22,23
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	21-23
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	21
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☐	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	20

Supplementary material 6: ITREMA questionnaire

1: DEMOGRAPHICS *(Source: NIDS wave 3)*

The following questions relate to the participant's demographics		
(1)	Gender	☐ Female ☐ Male
(2)	Date of Birth	DD/MMM/YYYY: ☐☐ ☐☐☐ ☐☐☐☐
(3)	Education	☐ None ☐ Grade ___ (specify 1-12) ☐ Technikon / College ☐ University
	Home language	_____

2: EMPLOYMENT & INCOME COMPOSITION *(Source: NIDS wave 3)*

The following questions relate to the participant's <u>personal</u> employment and income.		
Q4 (5)	Are you currently employed?	☐ Yes, employed ☐ Yes, self employed ☐ No, unemployed → Go to Q6 ☐ No, student → Go to Q6 ☐ No, retired → Go to Q6 ☐ No, disabled → Go to Q6 ☐ No, other → Go to Q6 Specify: _____ ☐ Refused → Go to Q6 ☐ Don't know → Go to Q6
Q5 (8)	What was your personal take home pay last month? (if no income received write 0)	_____ ☐ Refused ☐ Don't know
The following questions relate to the participant's <u>household</u> employment and income.		

Q6 (9, 10)	What are the sources of income for this household? (Select all applicable. For each field, fill out the total income for the whole household)	☐ Salaries/wages/commission (amount received per month: _____) ☐ Income from a business (amount received per month: _____) ☐ Remittance (money received from people living elsewhere) (amount received per month: _____) ☐ Pensions (amount received per month: _____) ☐ Other income sources e.g. rental income, interest (amount received per month: _____) No income → Go to Q11
Q7 (11)	Do you receive any of the listed financial support? (select all that apply)	☐ Old-age grant (60-74, R1200; 75+, R1220) ☐ Disability grant (<60, R1200) ○ Permanent disability ○ Temporary disablity ○ Don't know
		☐ Child support grant (0-16, R280) ☐ Care dependency grant (0-17, R1200) ☐ Foster child grant (<22, R770) ☐ War veterans grant (60+, R1220) ☐ Grant-in-aid (R250 and should have another grant) ☐ Social relief of distress ☐ Refused ☐ Don't know

3: HOUSEHOLD COMPOSITION & PARTNERSHIP STATUS *(Source: SAHANES)*

The following questions relate to the participant's household composition and partnership status		
Q8 (4)	What is your partnership status? (Select the answer that best fits the current situation. Please only select one)	☐ Married (since: _____ year) ☐ Life partner (since: _____ year) ☐ Living together >50% of the time (since: _____ year) ☐ Single (since: _____ year) ☐ Divorced (since: _____ year) ☐ Widowed (since: _____ year) ☐ Multiple partners (since: _____ year) Other (specify: _____)
Q9 (14)	How many persons live under your roof?	_____ Number
Q10 (15)	How do these people relate to you?	☐ Partner (number _____) ☐ Biological children (number _____)

		☐ Other children (number _____) ☐ Parent(s) (number _____) ☐ Parent(s) in law (number _____) ☐ Brothers/sisters (number _____) ☐ Grandparents (number _____) ☐ Other family (number _____) ☐ Non-relatives (number _____) ☐ Refused ☐ Don't know

4: FOOD SECURITY *(Source: SAHANES)*

The following questions relate to the availability of food in the participant's household		
Q11 (52)	Did your household run out of money to buy food during the past 12 months?	☐ Yes ☐ No → **Go to Q16** ☐ Don't know
Q12 (53)	Has it happened in the past 30 days?	☐ Yes ☐ No → **Go to Q14** ☐ Don't know
Q13 (54)	Has it happened 5 or more days in the past 30 days?	☐ Yes ☐ No ☐ Don't know
Q14 (55)	In the past 12 months, were there times when members of your household went hungry because there was not enough food in the house to eat?	☐ Yes ☐ No ☐ Don't know
Q15 (56)	Which were the months (in the last 12 months) in which you experienced a lack of food or money such that one or more members of your household had to go hungry?	☐ January ☐ February ☐ March ☐ April ☐ March ☐ April ☐ May ☐ June ☐ July ☐ August ☐ September ☐ October ☐ November ☐ December ☐ Don't know

5: ADHERENCE *(Source: ACTG)*

The following questions are about how the participant feels about starting to take ARV's.					
"These questions are about how people feel about starting to take ARV's. How sure are you that…"		*Not at All Sure*	*Somewhat Sure*	*Very Sure*	*Extremely Sure*
Q16 *(94)*	*You will be able to take all or most of the medication as directed?*	☐	☐	☐	☐
Q17 *(95)*	*The medication will have a positive effect on your health?*	☐	☐	☐	☐
Q18 *(96)*	*If you do not take this medication exactly as instructed, the HIV in your body will become resistant to HIV medication?*	☐	☐	☐	☐
"The following questions ask about your social support…"					
Q19 *(97)*	*In general, how satisfied are you with the overall support you get from your friends and family members?*	☐ *Very Dissatisfied* ☐ *Somewhat Dissatisfied* ☐ *Somewhat Satisfied* ☐ *Very Satisfied*			
Q20 *(98)*	*To what extent do your friends or family members help you remember to take your medication?*	☐ *Not At All* ☐ *A Little* ☐ *Somewhat* ☐ *A Lot* ☐ *Not Applicable*			

People may miss their medication for various reasons. Here is a list of possible reasons why the patient may have missed taking any medications **he/she was already taking** within the **past month**.					
"In the past month, how often have you missed taking your medication because you…"		*Never*	*Rarely*	*Sometimes*	*Often*
Q21 *(99)*	*Were away from home?*	☐	☐	☐	☐
Q22 *(100)*	*Were busy with other things?*	☐	☐	☐	☐
Q23 *(101)*	*Simply forgot?*	☐	☐	☐	☐
Q24 *(102)*	*Had too many pills to take?*	☐	☐	☐	☐
Q25 *(103)*	*Wanted to avoid side effects?*	☐	☐	☐	☐
Q26 *(104)*	*Did not want other notice you taking medication?*	☐	☐	☐	☐
Q27 *(105)*	*Had a change in daily Routine?*	☐	☐	☐	☐

Q28 *(106)*	*Felt like drug was toxic/harmful?*	☐	☐	☐	☐
Q29 *(107)*	*Fell asleep/slept through dose time?*	☐	☐	☐	☐
Q30 *(108)*	*Felt sick or ill?*	☐	☐	☐	☐
Q31 *(109)*	*Felt depressed/overwhelmed?*	☐	☐	☐	☐
Q32 *(110)*	*Had problem taking pills at a specified times (with meals, on empty stomach etc)?*	☐	☐	☐	☐
Q33 *(111)*	*Ran out of pills?*	☐	☐	☐	☐
Q34 *(112)*	*Felt good?*	☐	☐	☐	☐
Q35 *(113)*	*How often do you have difficulty in taking your medication on time? By "on time" we mean no mor than two hours before or after the time your doctor instructed you to take it. (Check one box)*	☐ *All of the time* ☐ *Most of the time* ☐ *Rarely* ☐ *Never*			
Q36	*On average how many days per week would you s that you missed at least one dose of your medicatio (Check one box)*	☐ *Every day* ☐ *4 – 6 days per week* ☐ *2 – 3 days per week* ☐ *Once a week* ☐ *Less than once a week* ☐ *Never*			
Q37	*When was the last time you missed taking any of y medications? (Check one box)*	☐ *within the past* ***week*** ☐ *1 – 2* ***week****s ago* ☐ *2 – 4* ***week****s ago* ☐ *1 – 3* ***months*** *ago* ☐ *More than 3* ***months*** *ago* ☐ ***Never***			

6: ACTUAL SUPPORT FROM HOUSEHOLD MEMBERS *(Source: NKPS)*

This segment is about support the participant receives from household members					
	"To what extent do persons in your household support you…"	*No support*	*A little support*	*A fair amount of support*	*A lot of support*
Q38	*In decisions about work or education*	1	2	3	4
Q39	*When you have worries or health problems*	1	2	3	4

Q40	*In your leisure time activities and social contacts*	1	2	3	4
Q41	*With all kinds of practical things you need to do*	1	2	3	4
Q42	*In personal matters that are on your mind*	1	2	3	4

7: ACTUAL FAMILY SUPPORT *(Source: NKPS)*

This segment is about support the participant receives from family members who do not live in the household					
	"To what extent do family members who do not live in your household support you…"	*No support*	*A little support*	*A fair amount of support*	*A lot of support*
Q43	*In decisions about work or education*	1	2	3	4
Q44	*When you have worries or health problems*	1	2	3	4
Q45	*In your leisure time activities and social contacts*	1	2	3	4
Q46	*With all kinds of practical things you need to do*	1	2	3	4
Q47	*In personal matters that are on your mind*	1	2	3	4

8: COPING ABILITIES *(Source: CISS-21)*

This segment is about how the participant reacts to various difficult, stressful or upsetting situations. Every possible reaction needs to be scaled from "never" to "always".						
	"During a difficult, stressful or upsetting situation, how often do you do the following…"	*Never*	*Rarely*	*Sometimes*	*Very often*	*Always*
Q48	*Take some time off and get away from the situation*	*1*	*2*	*3*	*4*	*5*
Q49	*Focus on the problem and see how I can solve it*	*1*	*2*	*3*	*4*	*5*
Q50	*Blame myself for having gotten into this situation*	*1*	*2*	*3*	*4*	*5*
Q51	*Treat myself to a favourite food or snack*	*1*	*2*	*3*	*4*	*5*
Q52	*Feel anxious about not being able to cope*	*1*	*2*	*3*	*4*	*5*
Q53	*Think about how I solved similar problems*	*1*	*2*	*3*	*4*	*5*

Q54	*Visit a friend*	*1*	*2*	*3*	*4*	*5*
Q55	*Determine a course of action and follow it*	*1*	*2*	*3*	*4*	*5*
Q56	*Buy myself something*	*1*	*2*	*3*	*4*	*5*
Q57	*Blame myself for being too emotional on the situation*	*1*	*2*	*3*	*4*	*5*
Q58	*Work to understand the situation*	*1*	*2*	*3*	*4*	*5*
Q59	*Become very upset*	*1*	*2*	*3*	*4*	*5*
Q60	*Take corrective action immediately*	*1*	*2*	*3*	*4*	*5*
Q61	*Blame myself for not knowing what to do*	*1*	*2*	*3*	*4*	*5*
Q62	*Spend time with a special person*	*1*	*2*	*3*	*4*	*5*
Q63	*Think about the event and learn from my mistakes*	*1*	*2*	*3*	*4*	*5*
Q64	*Wish that I could change what had happened or how I felt*	*1*	*2*	*3*	*4*	*5*
Q65	*Go out for a snack or meal*	*1*	*2*	*3*	*4*	*5*
Q66	*Analyze the problem before reacting*	*1*	*2*	*3*	*4*	*5*
Q67	*Focus on my general inadequacies*	*1*	*2*	*3*	*4*	*5*
Q68	*Phone a friend*	*1*	*2*	*3*	*4*	*5*

9: CAREGIVER TRUST (Source: The Helping Alliance – HAQ2)

The following statements are about the patient's relationship with the caregiver at Ndlovu Medical Centre. Please indicate to what extent the patient agrees or disagrees with the statement.							
"To what extent do you agree or disagree with the following statements"		*Strongly disagree*	*Disagree*	*Slightly disagree*	*Slightly agree*	*Agree*	*Strongly Agree*
Q69	*I feel I can depend upon the clinician.*	☐	☐	☐	☐	☐	☐
Q70	*I feel the clinician understands me.*	☐	☐	☐	☐	☐	☐
Q71	*At times I distrust the clinician's judgment.*	☐	☐	☐	☐	☐	☐
Q72	*I feel I am working together with the clinician in a joint effort.*	☐	☐	☐	☐	☐	☐
Q73	*I believe we have similar ideas about the nature of my problems.*	☐	☐	☐	☐	☐	☐
Q74	*I generally respect the clinician's views about me.*	☐	☐	☐	☐	☐	☐
Q75	*I like the clinician as a person.*	☐	☐	☐	☐	☐	☐
Q76	*A good relationship has formed with my clinician.*	☐	☐	☐	☐	☐	☐
Q77	*The clinician appears to be experienced in helping people.*	☐	☐	☐	☐	☐	☐

Q78	*I believe the clinician likes me as a person.*	☐	☐	☐	☐	☐	☐
Q79	*At times the clinician seems distant.*	☐	☐	☐	☐	☐	☐

10: HEALTH LITERACY *(Source: BEHKA-HIV)*

The following questions are used to check the participant's knowlegde of HIV. Let patients answer on their own, without giving hints.				
"We would like to know if patients are familiar with two HIV terms: "CD4-count" and "viral load". Would you mind if I ask you a few questions about that?"				
Q80	*What is a CD4-count?*			
Q81	*Is the goal of ARV's to make the CD4-count go UP or DOWN?*	☐ *UP*	☐ *DOWN*	
Q82	*What is a viral load?*			
Q83	*Is the goal of ARV's to make the viral load go UP or DOWN?*	☐ *UP*	☐ *DOWN*	
Q84	*What medicines are you currently taking to treat HIV?*			
"Please tell me if you agree, are not sure, or disagree with the following statements."				
Q85	*I don't take my ARV's when they make me feel bad.*	☐ *Agree*	☐ *Unsure*	☐ *Disagree*
Q86	*I don't take my ARV's when I am too tired.*	☐ *Agree*	☐ *Unsure*	☐ *Disagree*
Q87	*I don't take my ARV's when I am feeling down or low.*	☐ *Agree*	☐ *Unsure*	☐ *Disagree*
Q88	*I don't take my ARV's because it tastes bad.*	☐ *Agree*	☐ *Unsure*	☐ *Disagree*
Q89	*I don't take my ARV's when I feel good.*	☐ *Agree*	☐ *Unsure*	☐ *Disagree*

11: MENTAL HEALTH *(Source: PHQ-9)*

The following questions ask about symptoms. For each symptom, the symptom frequency must be given.						
"Over the last 2 weeks, how often have you been bothered by any of the following problems?"		*Not at all*	*Several days*	*More than half the days*	*Nearly every day*	*Refuse*
Q90 (18)	*Little interest or pleasure in doing things*	☐	☐	☐	☐	☐
Q91 (19)	*Feeling down, depressed, or hopeless*	☐	☐	☐	☐	☐
Q92 (20)	*Trouble falling or staying asleep, or sleeping too much*	☐	☐	☐	☐	☐
Q93 (21)	*Feeling tired or having little energy*	☐	☐	☐	☐	☐
Q94 (22)	*Poor appetite or overeating*	☐	☐	☐	☐	☐

Q95 *(23)*	*Feeling bad about yourself — or that you are a failure or have let yourself or your family down*	☐	☐	☐	☐	☐
Q96 *(24)*	*Trouble concentrating on things, such as reading the newspaper or watching television*	☐	☐	☐	☐	☐
Q97 *(25)*	*Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual*	☐	☐	☐	☐	☐
Q98 *(26)*	*Thoughts that you would be better off dead or of hurting yourself in some way*	☐	☐	☐	☐	☐

12: STIGMATIZATION (Source: AIDS-related stigma scale)

The following questions relate to stigma. Ask the participant if he/she agrees with these statements					
"Do you agree with the following statements?"		*Strongly disagree*	*Disagree*	*Agree*	*Strongly Agree*
Q99 *(34)*	*People who have AIDS are dirty*	☐	☐	☐	☐
Q100 *(35)*	*People who have AIDS are cursed*	☐	☐	☐	☐
Q101 *(36)*	*People who have AIDS cannot be trusted*	☐	☐	☐	☐
Q102 *(37)*	*People who have AIDS are like everybody else*	☐	☐	☐	☐
Q103 *(38)*	*People who have AIDS should be ashamed*	☐	☐	☐	☐
Q104 *(39)*	*People who have AIDS have nothing to feel guilty about*	☐	☐	☐	☐
Q105 *(40)*	*Most people become HIV positive by being weak or foolish*	☐	☐	☐	☐
Q106 *(41)*	*It is safe for people who have AIDS to work with children*	☐	☐	☐	☐
Q107 *(42)*	*People who have AIDS must expect restrictions on their freedom*	☐	☐	☐	☐
Q108 *(43)*	*A person with AIDS must have done something wrong and deserves to be punished*	☐	☐	☐	☐
Q109 *(44)*	*People who have HIV should be isolated*	☐	☐	☐	☐
Q110 *(45)*	*People who have AIDS should not be allowed to work*	☐	☐	☐	☐
Q111	*I do not want to be friends with someone who has HIV/AIDS*	☐	☐	☐	☐
Q112 *(46)*	*Would you care for a family member with HIV/AIDS?*	☐ *Yes* ☐ *No*			
Q113 *(47)*	*Would you mind if people knew if your family member had HIV/AIDS*	☐ *Yes* ☐ *No*			

13: SEXUAL PARTNERS & TRANSACTIONAL SEX *(Source: UNAIDS sexual networks)*

These questions are about the patient's sexual partners in the last 12 months		
Q114 *(48)*	*How many sexual partners have you had in the last 12 months?*	_____ *Number*
Q115 *(50)*	*How many sexual partners do you currently have?*	_____ *Number*

*"I would like to ask you about people you had sex with **in the last 12 months**. Please only give this information if you are comfortable giving it. We will not disclose any of the information you give us."*									
Q116	*What are the partners initials?*	*1* _____	*2* _____	3 _____	4 _____	5 _____	6 _____	7 _____	8 _____
Q117 *(49)*	*What is the partners age?*								
Q118	*How many times in the last month did you have sex with this person?*	_____	_____	_____	_____	_____	_____	_____	_____
Q118	*How long has the relationship been going on?* *Years* *Months* *Days*	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____
Q120	*How often do you have sex with this partner without a condom?* Always 1 Often 2 Half of the time 3 Rarely 4 Never 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Q121 *(51)*	*Do you ever have sex in exchange for money or goods?*	☐ *Never* ☐ *Sometimes* ☐ *Often* ☐ *Always*							

14: SUBSTANCE ABUSE (Source: CHAMP study questionnaire)

These questions ask about the participant's use of drug and alcohol						
		Never	***Less than monthly***	***Monthly***	***Weekly***	***Daily / almost daily***
Q121	*How often do you have a drink containing alcohol?*					

Q122	*Do you have six or more drinks on one occasion?*					
Q123	*In the past year were you unable to remember what happened the night before because of your drinking?*					

Q124	*Have you ever used any of the following …* *You may choose more than one answer*	*Dagga*	
		Benzene or petrol	
		Mandrax	
		Injected drugs (drugs that you inject)	
		Nyaope	
		Sniff glue	
		Other drug	

CHAPTER 3

Antiretroviral therapy uptake and predictors of virological failure in patients with HIV receiving first-line and second-line regimens in Johannesburg, South Africa: a retrospective cohort data analysis

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ABSTRACT

Objective This study described the demographics, treatment information and identified characteristics associated with virological failure and being lost to follow- up (LTFU) for patients with HIV on first- line and second- line antiretroviral therapy (ART) regimens in a large South African cohort.

Design A quantitative retrospective cohort study using secondary data analysis.

Setting Seven Johannesburg inner city facilities.

Participants Unique records of 123 002 people with HIV receiving ART at any point in the period 1 April 2004 to 29 February 2020 were included.

Measures Demographic characteristics, ART status, CD4 count information and retention status were collected and analysed as covariates of outcomes (viral load (VL) and LTFU).

Results Of the total study patients, 95% (n=1 17 260) were on a first-line regimen and 5% (n=5742) were on a second-line regimen. Almost two-thirds were female (64%, n=79 226). Most patients (60%, n=72 430) were initiated on an efavirenz-based, tenofovir disoproxil fumarate-based and emtricitabine-based regimen (fixed-dose combination). 91% (n=76 737) achieved viral suppression at least once since initiating on ART and 60% (n=57 981) remained in care as at the end of February 2020. Patients from the community health centre and primary healthcare clinics were not only more likely to be virally suppressed but also more likely to be LTFU. Patients on second-line regimens were less likely to reach viral suppression (adjusted OR (aOR)=0.26, CI=0.23 to 0.28) and more likely to be LTFU (aOR=1.21, CI=1.09 to 1.35). Being older (≥25 years) and having a recent CD4 cell count≥100 cells/µL were predictors of viral suppression and retention in patients on ART.

Conclusion Patients on first-line regimens had higher VL suppression rates and were more likely to remain in care than those on a second-line regimen. Being younger and having low CD4 cell counts were associated with poor outcomes, suggesting priority groups for ART adherence support.

Strengths and limitations of this study

► This is one of the largest studies to date from the South African national HIV treatment programme reporting on antiretroviral therapy uptake, virologic failure and retention in care.

► Data are presented from 2004, the inception of the national HIV treatment programme in the public
health system setting.

► The study identified groups for prioritising interventions to improve clinical and retention outcomes.

► The analyses were completed for only 7 of over 120 health facilities in one South African metropolitan municipality.

► Due to data inconsistencies, we could not accurately calculate time to viral load suppression or failure.

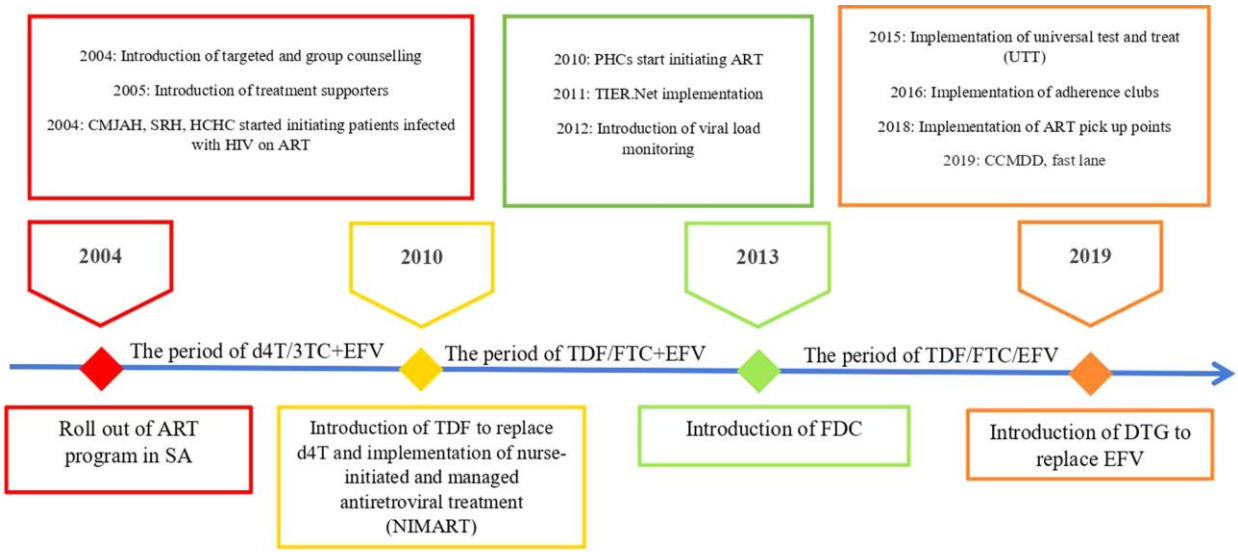
INTRODUCTION

Antiretroviral therapy (ART) is critical to maintain HIV viral load (VL) suppression, improve immunologic function and reduce HIV-related morbidity and mortality [1,2]. Therefore, provision of ART to people with HIV has continued to be scaled up, with an estimated 24 [5]. million people with HIV taking ART globally in 2019 [3,4]. South Africa contributes about 20% (4.8 million) of the global number of HIV-positive people accessing ART [5,6].

Many countries, including South Africa, follow the WHO recommendations for first-line and subsequent-line ART [2,7]. South Africa replaced stavudine (d4T) with tenofovir disoproxil fumarate (TDF) in 2010 and is transitioning from efavirenz (EFV)-based first-line treatments and protease inhibitor (PI)-based second-line treatments to dolutegravir (DTG)-based regimens (figure 1); all regimens include emtricitabine (FTC) or lamivudine (3TC) [7-9].

In 2019, an estimated 15%–20% of people on first-line ART and up to 30% of people on second-line ART in the South African HIV treatment programme experienced virological failure [10-13]. Further, up to approximately 40% of people on first-line ART and up to 20% of people with HIV on second-line ART were lost to-follow- up (LTFU), defined as patients who missed their clinic appointment by over 90 days or did not collect their ART without being confirmed as having died or transferred out [10-14]. Identifying factors which predict high risk of treatment failure and/or non-retention in care on either first-line or second-line ART will facilitate the development of mitigation interventions in these groups.

This study describes the overall demographics and treatment information of a large cohort initiating first-line and second-line ART regimens in central Johannesburg. It further identifies demographic and clinical characteristics that predict virological failure and LTFU.



Period (years)	CD4 cell count threshold	Average baseline CD4 cell count (at ART initiation) for the study cohort
2004-2010	≤200 cells/ mm3	156 cells/ mm3
2011-2014	≤350 cells/mm3	209 cells/ mm3
2015	≤500 cells/ mm3	284 cells/ mm3
2016-To date	No CD4 cell count threshold	331 cells/ mm3

Figure 1 Evolution of ART and changes in CD4 cell count thresholds in South Africa

Abbreviations: ART, antiretroviral therapy; d4T, stavudine; DTG, dolutegravir; EFV, efavirenz; FDC, fixed-dose combination of TDF/FTC//EFV; FTC, emtricitabine; PHCs, primary healthcare clinics; SA, South Africa; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

METHODS

Study design

TIER.Net is the ART patient and data management system for the digitisation of paper registers that was developed by the University of Cape Town Centre for Infectious Disease Epidemiology and Research, in collaboration with the South African National Department of Health (SA NDoH) [15-16]. TIER.Net allows public health facilities to record and monitor patients on ART and tuberculosis treatment across the continuum of care [15,16]. The system commenced roll out in 2011 and full functionality/sign off required all records to be back captured so that the system could then be used prospectively. To account for files that may have been misplaced, data were also captured from the ART longitudinal paper-based registers in use at all public health facilities prior to the TIER.Net electronic version being implemented. The information retrieved from the ART longitudinal paper-based register included patient folder or unique number, sex, ART start date, CD4 at baseline, ART regimen at baseline, duration on ART, retention status, date of ART switch and current ART regimen. Time taken for facilities to be signed off was dependent on the resources available to capture and clean the data. Data quality was completed using standard operating procedures provided by the SA NDoH. This was a quantitative retrospective cohort study using secondary analysis of data on people

with HIV taking ART (18 years and older) recorded in the TIER.Net database and an expansion of a study conducted on patients receiving second-line ART in the Johannesburg inner city (region F) [10].

Setting

Seven high volume public health facilities that were operational at the time of data extraction and had a functional TIER.Net system in the Johannesburg inner city (subdistrict F) were included in the study. This included two hospitals, one community health centre (CHC) and four primary healthcare clinics (PHCs).

Brief description and frequency of ART visits

All health facilities provide ART services as per WHO and South African ART guidelines [2,17]. Following an HIV diagnosis, a package of HIV and ART care services is offered to ensure timely linkage to care. This includes adherence counselling, clinical assessment (monitoring of VL, CD4 cell count and creatine), ART initiation and any psychosocial support if needed. Importantly, clinic visits are different for each patient in terms of clinical monitoring, ART medication and adherence support offered. For stable or virally suppressed patients, clinic visits can be scheduled between 3 and 6 months in line with WHO recommendations [17]. As part of differentiated care patients may attend adherence clubs or receive ART outside of conventional health facilities and these visits are likely to occur semi-annually. Patients who have an unsuppressed HIV VL mainly attend monthly clinic visits and have their VL monitored more frequently (VL repeated in 2 months following the first unsuppressed VL reading) [2,17]. In most cases, patients are provided with sufficient ART to last for the period between clinic visits (exceptions linked to medication shortages in which the patient will return to the facility only for a medication collection and not wait in line for a clinical consultation). Patients who are unable to attend their next appointment are encouraged to communicate with health facilities to reschedule within the first 3 months of the missed appointment. With the current systems and non-linked TIER.Net, it is difficult to control patients who leave one health facility to another without appropriate or official transfer-out information (these patients are regarded as self-transfer-out patients). Self-transfer-out negatively affects LTFU rates as most of these patients are active in another facility while regarded as LTFU in their original health facility.

Record selection and data extraction

Study data were extracted in March 2020. Records of people with HIV who started ART between 1 April 2004 (the inception of the South African national HIV treatment programme in the public health system setting) and 29 February 2020 from the seven public health facilities were included in the study. Overall, 233 593 records were available in the TIER.Net database. Records were excluded as follows: 104 757 records of patients who were not on ART; 406 records of patients who were initiated prior to April 2004; 3739 records of patients who were younger than 18 years; 1628 records of patients on third-line ART and 51 records of patients with inaccurate regimen information captured.

Overall, 123 002 records of people with HIV taking ART (first-line regimen and second-line regimen) were included (figure 2). TIER.Net data were exported to Microsoft Excel 2016 Professional Plus. Extracted variables included: treatment facility, sex, patient's age at ART start, patient's current age, ART start date, baseline ART regimen, last prescribed ART regimen, CD4 cell count at start of ART, most recent CD4 cell count (the last recorded CD4 cell count result), most recent VL count (the last recorded VL result) and retention in care status.

The recoding of continuous variables, such as CD4 cell count and VL count, into categorical variables was informed by WHO guidelines and thresholds.17–21 The CD4 cell count values were categorised into the following ranges: <100 cells/µL, 101–200 cells/µL, 201–350 cells/µL, 351–500 cells/µL and above 500 cells/µL [17-19].

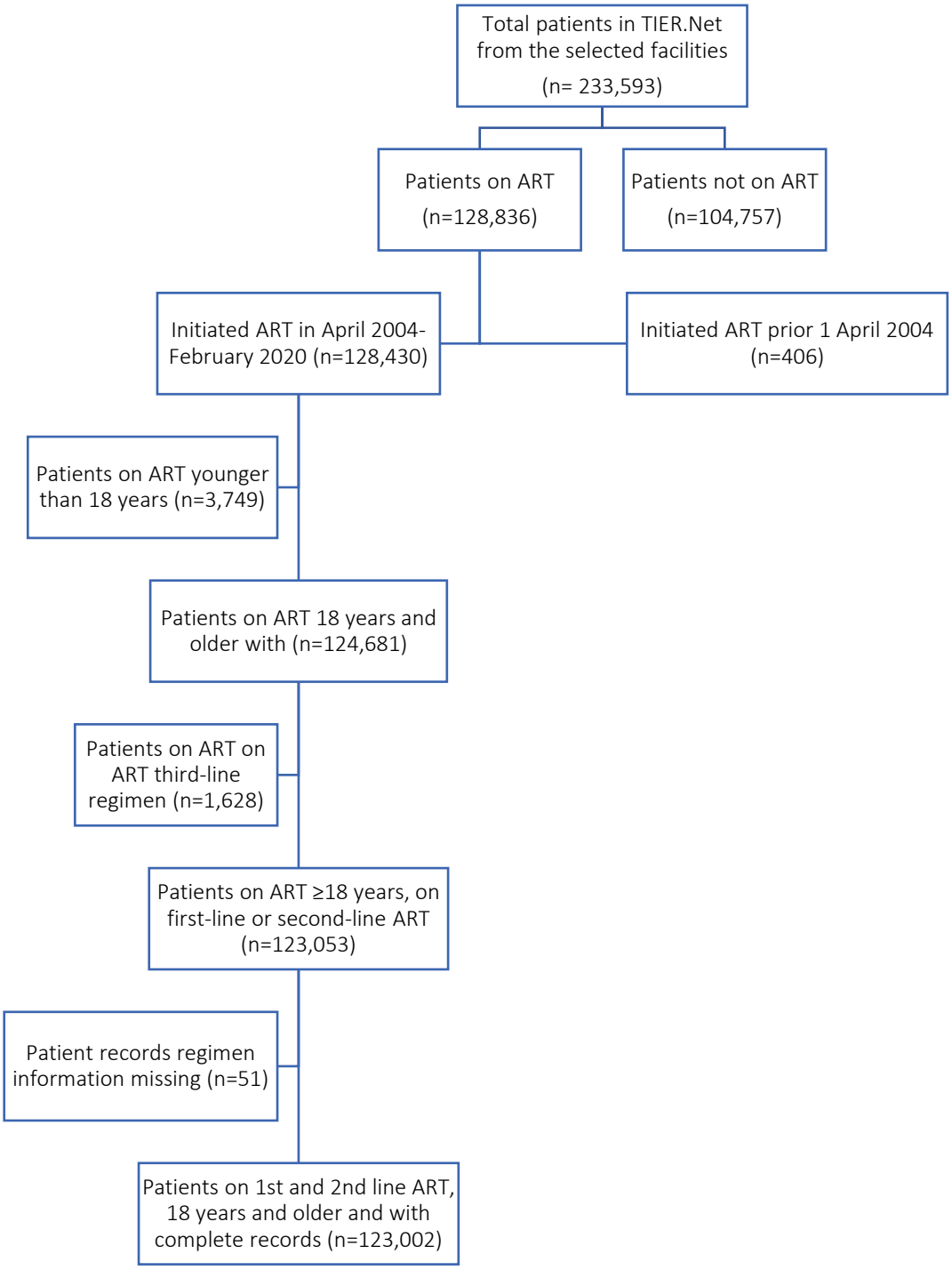


Figure 2 Flow diagram for the selection of study records

Notes: ART, antiretroviral therapy. Note: Patients not on ART include (1) patients who did not qualify to commence ART because of guideline mandated CD4 cell count thresholds (prior to the test and treat strategy); (2) decision not to start ART made by a clinician and (3) patients who did not complete pre-treatment procedures, such as counselling.

Outcomes

VL count was categorised into suppressed (<1000 copies/mL) or unsuppressed (≥1000 copies/mL) [20,21]. Virological failure, according to the WHO, is defined as two consecutive VLs≥1000 HIV RNA copies/mL repeated within 2 months [22]. The status on retention in care for patients was categorised into active in care, LTFU, transferred out or recorded dead. For this study, LTFU was defined as having missed a scheduled medical appointment by 90 days or more, as defined by the SA NDoH. Unrecorded LTFU, transfer out and deaths were all recorded as LTFU as defined by the SA NDoH [14].

Data analysis

Data were analysed using Stata V.15.1 (StataCorp, USA). Continuous demographic data were summarised and analysed using median and IQR statistics, where appropriate, and then grouped into categories. Transfers out were excluded in the calculation of retention rates, since these patients were not expected to be in care in the included facilities, however deaths and LTFU were included [14,23,24]. Pearson χ^2 tests were used to assess associations between outcome variables (VL and retention in care status) and demographic characteristics (age at start of ART, current age, sex, health facility). Univariate and multivariable logistic regression models of the outcome variables were constructed to control for confounders and identify independent predictors. We also fitted multivariable logistic regression models with individual fixed effects. Associations with these predictors are reported as unadjusted (crude) and adjusted ORs (aORs), with 95% CIs and p values; p values smaller than 0.05 are considered statistically significant. To assess predictors of retention, survival analysis, using the Kaplan-Meier estimator, was performed for LTFU (patients who are no longer in care at the health facility and were not confirmed as transferred out or died) category.

Ethics approval

We obtained ethical clearance from the University of the Witwatersrand Human Research Ethics Committee (M190641). Departmental approval was granted by the Johannesburg Health District (DRC Ref: 2019-10-005. National Health Research Database reference number: GP_201910_031). There was neither interaction with the patients nor access to their individual medical records. An anonymized data extract was used for the analyses.

Patient and public involvement

Patients and the public were not involved in the design and conduct of the study.

RESULTS

In total, records of 123 002 people with HIV were included (95% (n=117 260) on a first-line regimen and 5%, (n=5742) on a second-line regimen). Table 1 shows participants' characteristics by ART regimen. Almost two-thirds of patients whose records were included were women (64%, n=79 226).

Patients' median age at the start of ART was 33 years (IQR 28–39 years); at the time of data extraction, patients' average age was 38 years (IQR 32–45 years). At ART start, 15% patients (n=18 476) were 25 years or younger, 6% patients (n=6945) were 50 years and above, and this latter group increased to 14% patients (n=17 323) at the time of data extraction. The average duration on ART was 64 months (IQR 31–105 months), with patients on a first-line regimen having shorter treatment durations (62 months, 30–103 months) than those on a second-line regimen (107 months, 75–131 months). The average CD4 cell count of patients initiating ART at different points in time increased steadily, from 156 cells/µL between 2004 and 2010 to 209 cells/µL between 2011 and 2014, 284 cells/µL in 2015, 329 cells/µL between 2016 and 2018 and 336 cells/µL between 2019 and 2020. Overall, 98 626 patients had a recent CD4 cell count recorded in the TIER.Net database. Of these, 27% (n=26 997) had CD4 cell counts>500 cells/µL (16% increase from baseline CD4 cell count) at their most recent measurement, while13% (n=12 432) had CD4 cell count≤100 cells/µL representing a 12% decrease from the baseline CD4 cell count. At the time of the data extraction for this study, just over 1% of people with HIV receiving ART were on DTG (n=1479); 792 patients were initiated on DTG as new patients and 687 switched from EFV to DTG. Of the total cohort, 47% (n=57 981) were still active in care, with 32% (n=39 195) LTFU, 20%, (n=24 931) transferred out and less than a percent recorded as dead (0.7%, n=895). After combining the few known deaths with the LTFU (which already included unrecorded or self-transfer-out), 32.6% (40 090) patients were lost from care, unreported transfers or deaths.

Table 1: Distribution of demographic and clinical characteristics by ART regimen.

	Total (N= 123,002)		First-line regimen (N= 117,260)		Second-line regimen (N= 5,742)	
Characteristic	**Median**	**Inter-quartile range**	**Median**	**Inter-quartile range**	**Median**	**Inter-quartile range**
Age at ART start (N= 123,002)	33 years	28-39 years	33 years	28-39 years	33 years	28-39 years
Current age* (N= 123,002)	38 years	32-45 years	38 years	32-45 years	41 years	36-47 years
Duration on ART (N= 123,002)	64 months	31-105 months	62 months	30-103 months	107 months	75-131 months
CD4 cell count at start of ART (N=95,697)	200 cells/ul	101-337 cells/ul	205 cells/ul	106-342 cells/ul	116 cells/ul	44-204 cells/ul
Most recent CD4 cell count* (N= 98,626)	336 cells/ul	188-522 cells/ul	337 cells/ul	190-523 cells/ul	318 cells/ul	154-516 cells/ul
Viral load (N= 84,252)	124 copies/ml	45-124 copies/ml	124 copies/ml	44-124 copies/ml	124 copies/ml	49-231 copies/ml
<1000 copies/ml	124 copies/ml	40-124 copies/ml	124 copies/ml	40-124 copies/ml	124 copies/ml	39-124 copies/ml
≥1000 copies/ml	36883 copies/ml	7090-155883 copies/ml	37900 copies/ml	7225-159021 copies/ml	32271 copies/ml	6110-140000 copies/ml
Characteristic	**Frequency**	**Percentage**	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Facility (N= 123,002)						
Charlotte Maxeke Hospital	11,545	9.39	10,309	8.79	1,236	21.53
Hillbrow CHC	54,328	44.17	51,103	43.58	3,225	56.17
Jeppe Clinic	14,765	12.00	14,647	12.49	118	2.06
Malvern Clinic	9,621	7.82	9,512	8.11	109	1.90
Rosettenville Clinic	8,216	6.68	8,138	6.94	78	1.36
South Rand Hospital	10,385	8.44	8,138	8.33	613	10.68
Yeoville Clinic	14,142	11.50	13,779	11.75	363	6.32
Age at ART start (N= 123,002)						
<25 years	18,476	15.02	17,597	15.01	879	15.31
25-34 years	51,649	41.99	49,287	42.03	2,362	41.14
35-49 years	45,932	37.34	43,749	37.31	2,183	38.02
50+ years	6,945	5.65	6,627	5.65	318	5.54
Current age* (N= 123,002)						
<25 years	7,875	6.40	7,544	6.43	331	5.76
25-34 years	33,372	27.13	32,555	27.76	817	14.23
35-49 years	64,432	52.38	60,903	51.94	3,529	61.46
50+ years	17,323	14.08	16,258	13.86	1,065	18.55
Sex (N= 123,000)						
Female	79,226	64.41	75,752	64.60	3,474	60.50
Male	43,774	35.59	41,506	35.40	2,268	39.50

Total duration on ART (N= 123,002)						
<5 years	48,575	39.49	47,765	40.73	810	14.11
5-9 years	45,791	37.23	43,691	37.26	2,100	36.57
≥10 years	28,636	23.28	25,804	22.01	2,832	49.32
Baseline CD4 cell count at start of ART (N=95,697)						
≤100 cells/µl	23,764	24.83	21,731	23.83	2,033	45.00
101-200 cells/µl	24,190	25.28	22,873	25.09	1,317	29.15
201-350 cells/µl	25,757	26.92	25,005	27.42	752	16.64
351-500 cells/µl	11,318	11.83	11,077	12.15	241	5.33
>500 cells/µl	10,668	11.15	10,493	11.51	175	3.87
Most recent CD4 cell count* (N=98,626)						
≤100 cells/µl	12,432	12.61	11,595	12.40	837	16.39
101-200 cells/µl	14,248	14.45	13,454	14.39	794	15.55
201-350 cells/µl	24,988	25.34	23,845	25.50	1,143	22.39
351-500 cells/µl	19,961	20.24	18,984	20.30	977	19.13
>500 cells/µl	26,997	27.37	25,642	27.42	1,355	26.54
Viral load (N= 84,252)						
<1000 copies/ml	76,737	91.08	72,451	91.79	4,286	80.61
≥1000 copies/ml	7,515	8.92	6,484	8.21	1,031	19.39
DTG based regimen (N= 123,002)						
DTG based regimen	1,479	1.20	1,460	1.25	19	0.33
Without DTG	121,523	98.80	115,800	98.75	5,723	99.67
Retention status (N= 123,002)						
Active in care	57,981	47.14	54,898	46.82	3,083	53.69
Deceased	895	0.73	830	0.71	65	1.13
LTFU	39,195	31.87	37,588	32.06	1,607	27.99
Transferred/moved out	24,931	20.27	23,944	20.42	987	17.19

Notes: Current age = patient's age when data were extracted for the analysis from TIER.Net; Most recent CD4 cell count = most recent CD4 cell count available in the database.
Abbreviations: N, number; ART, antiretroviral therapy; LTFU, lost to follow up; DTG, dolutegravir.

ART initiations and LTFU

The number of people starting ART are presented as annual totals in **figure 3** and by regimen in **table 2**. The average annual number of ART initiations between 2004 and 2010 was 4092. There was a steady annual increase in the total number of people with HIV initiating ART between 2004 (n=840) and 2010 (n=8720), the period of d4T/3TC+EFV combination as the preferred first-line regimen. The average annual LTFU rate between 2004 and 2010 was 30%. The average annual number of ART initiations increased to 8772 patients per year between 2011 and 2013 (the period of TDF/3TC/EFV combination as a preferred first-line regimen), with an average of 35% LTFU rate in this period.

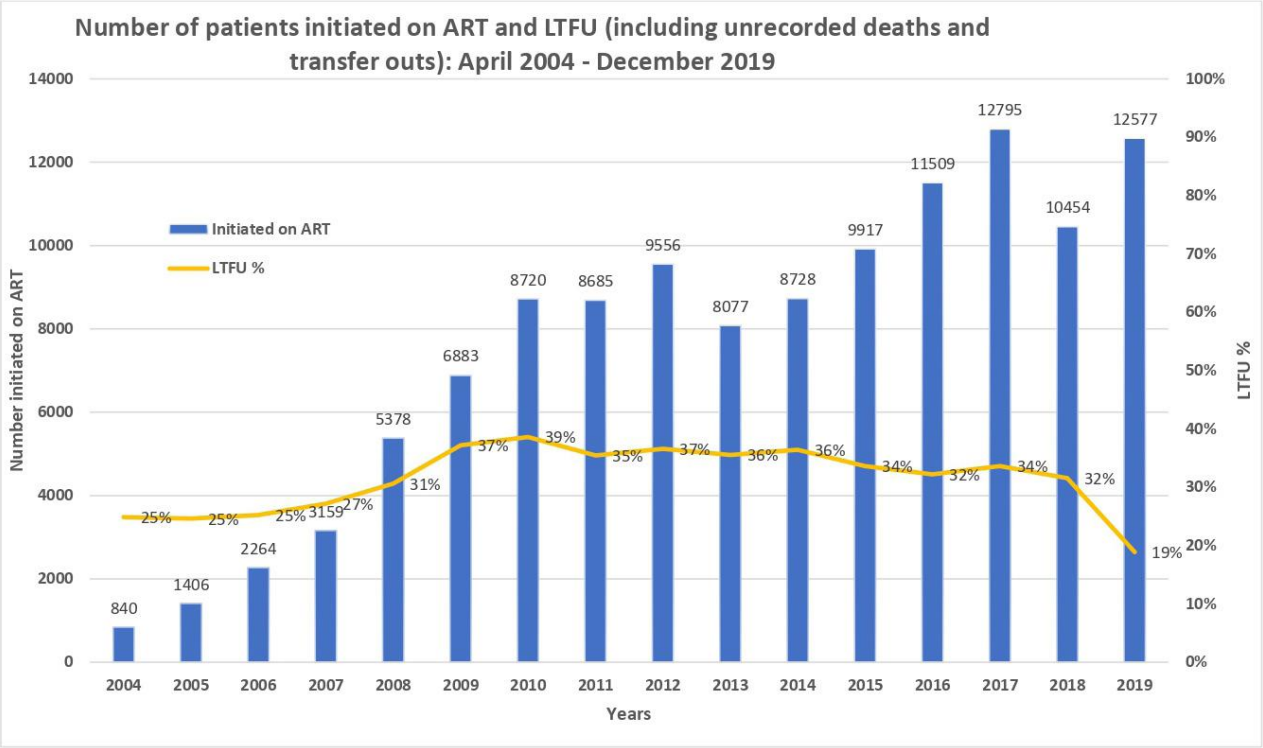


Figure 3 Numbers of ART new initiation and LTFU rate over time in the seven health facilities in subdistrict F. ART, antiretroviral therapy; LTFU, lost to follow-up.

Note: LTFU rates were calculated using the proxy denominator of ART initiation in the same period. LTFU also include unaccounted for deaths and transfers. A large proportion of those LTFU are in care elsewhere or dead.

Table 2: Number of people with HIV initiated on various antiretroviral drugs by calendar year.

CD4 cell count eligibility thresholds		≤200 cells/µl period (2004-2010)							≤350 cells/µl period (2011-2014)				≤500 cells/µl period (2015)	Universal Test and Treat (CD4 cell count not required as an eligibility criteria					
		Roll out of ART program in SA						Introduction of TDF			Introduction of FDC						Introduction of DTG		
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020 (end date: 29 Feb)	Total
Baseline ART	**First NRTI**																		
	TDF	74	136	215	416	715	871	4926	7515	8447	7537	8404	9658	11241	12311	10228	12463	2044	**97201**
	d4T	662	1119	1758	2296	3990	5585	3295	672	539	243	69	35	22	11	5	0	3	**20304**
	AZT	94	131	244	317	401	350	302	305	447	168	127	120	103	78	45	35	0	**3267**
	ABC	4	6	4	12	18	12	79	103	101	121	121	100	139	157	152	73	7	**1209**
	Second NRTI																		
	FTC	38	57	92	207	392	266	372	679	869	5157	7984	9397	10938	12476	10195	12396	1632	**73147**
	3TC	786	1331	2120	2830	4723	6539	8228	7912	8658	2911	737	516	565	311	253	175	421	**49016**
	ddI	9	4	10	4	9	11	2	4	4	1	1	1	1	1	0	0	1	**63**
	NNRTI																		
	EFV	720	1174	1773	2313	3808	4894	6488	6810	7990	7528	8476	9745	11384	12244	10276	12489	1605	**109717**
	NVP	90	186	407	665	1217	1764	1943	1648	1424	428	168	104	44	39	42	11	2	**10182**
	InSTI																		
	DTG	0	0	0	0	0	0	0	1	1	0	0	0	0	265	43	36	446	**792**
	RAL	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	**4**
	PIs																		
	LPV/r	21	30	39	56	93	129	145	125	114	114	75	61	73	72	81	28	1	**1257**
	ATV/r	0	0	3	1	1	1	1	0	0	0	0	2	2	12	5	6	0	**34**
	RTV[1]	3	2	1	6	4	29	23	12	5	0	1	0	2	1	1	0	0	**90**

Abbreviations: ART, antiretroviral therapy; SA, South Africa; TDF, tenofovir; FDC, fixed dose combination; DTG, dolutegravir; NRTI, nucleoside reverse transcriptase inhibitor; d4T, stavudine; AZT, zidovudine; ABC, abacavir; FTC, emtricitabine; 3TC, lamivudine; NNRTI, non-nucleoside reverse transcriptase inhibitor; ddI, didanosine; EFV, efavirenz; NVP, nevirapine; InSTI, integrase strand transfer inhibitor; RAL, raltegravir; PI, protease inhibitor; LPV/r, ritonavir-boosted lopinavir; ATV, ritonavir-boosted atazanavir; RTV, ritonavir.

Note: [1]There is a possibility of misreporting on TIER.Net with RTV data. Complexity of combination with ATV as well as double dosing for TB. No patient is given RTV alone if adult.

Antiretroviral drugs

Of the total patients initiated on ART between 2004 and 2020, 12% (n=15 074) were initiated on the d4T/3TC+EFV combination, 16% (n=19 105) were initiated on TDF/3TC/EFV combination and 59% (n=72 430) on FDC (TDF/FTC/EFV). Only 0.4% (n=451) were initiated on the tenofovir/lamivudine/dolutegravir regimen (TDF/3TC/DTG). Zidovudine accounted for 3% (n=3267) of regimens over the 16-year period. Ritonavir-boosted lopinavir (LPV/r) was the most used PI in this cohort with 91% (n=1257) of patients who started on a PI-based regimen being initiated on LPV/r.

Of patients with a completed VL on record (n=84 252), 91% (n=76 737) had achieved viral suppression, defined as ≤1000 copies/mL, at least once during treatment. The rate of VL suppression was 92% (n=72 451) for patients on a first-line regimen and 81% (n=4286) for patients on a second-line regimen.

Retention rates

Of all 1 23 002 patients on ART, 47% (n=57 981) remained in care at the initiating facility. The retention rate was 47% (n=54 898) among patients on a first-line regimen and 54% (n=3083) among patients on a second-line regimen. After removing transferred-out patients, leaving a total of 98 071 patients, the overall retention rate was 60% (59% among patients on a first-line regimen and 65% among patients on a second-line regimen). Survival analysis showed a steady decline in retention in care for both first-line and second-line regimens **(figure 4).** There was a higher decline in retention in care for patients on a first-line regimen from the start of ART throughout the treatment span than among those on a second-line regimen. These proportions even out after 15 years.

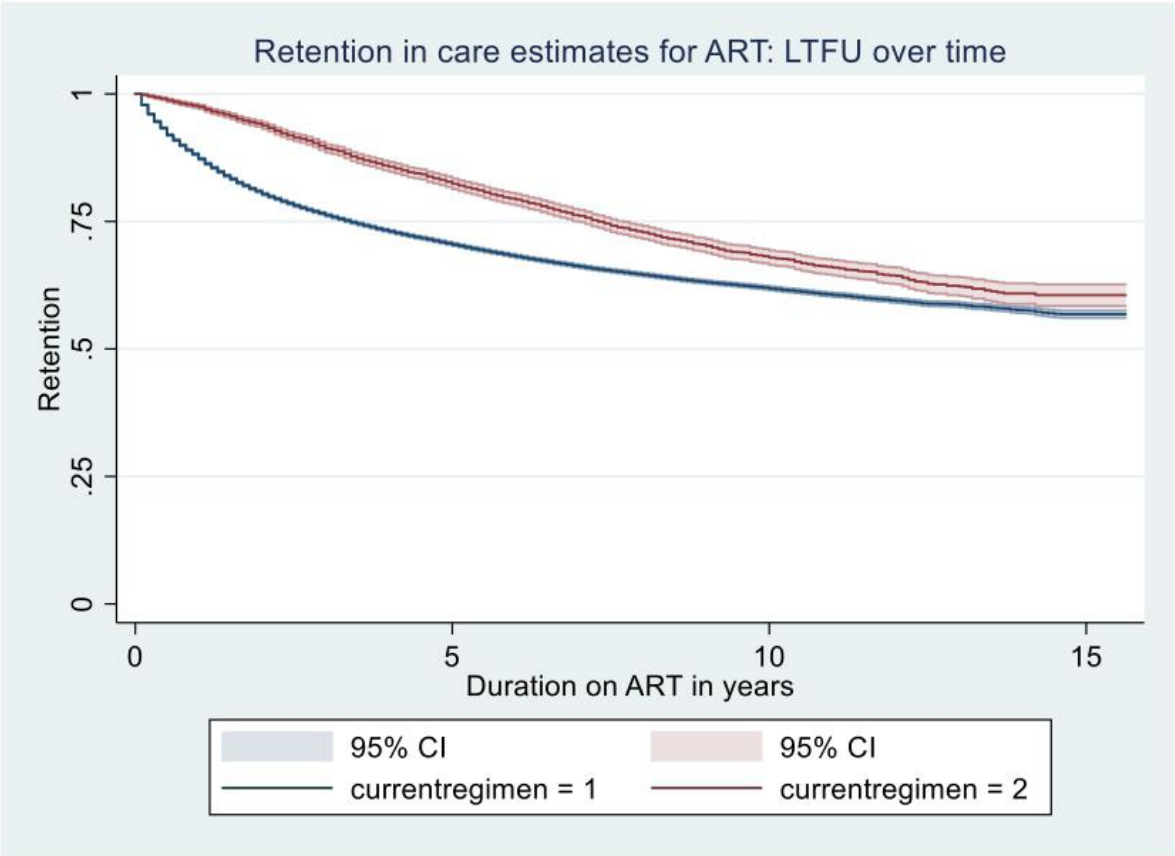


Figure 4 Survival analysis: retention over time for patients on a first-line and second-line antiretroviral therapy regimen. LTFU=lost to follow-up

Factors associated with VL suppression and LTFU

Table 3 shows findings of univariate and multivariable logistic regression analyses of current ART regimen and clinical characteristics with outcome variables (VL and LTFU). VL suppression was associated with ART regimen, with patients on the second-line regimen less likely than those on a first-line regimen to achieve VL suppression (aOR=0.26, CI=0.23 to 0.28). Regimen was also a predictor of retention in care status, where patients on a second-line regimen were more likely than those receiving a first-line regimen to be LTFU (aOR=1.21, CI=1.09 to 1.35). Patients on a fixed-dose combination were more likely to be virally suppressed (aOR=1.42, CI=1.26 to 1.59) and were also less likely to be LTFU (aOR=0.017, CI=0.015 to 0.019) than those on d4T/3TC+EFV. Likewise, patients on TDF/3TC/EFV were less likely to be LTFU than patients on d4T/3TC+EFV (aOR=0.14, CI=0.12 to 0.15). Level of care was associated with VL and being LTFU, with patients from the CHC (aOR=2.20, CI=2.02 to 2.39) and PHCs (aOR=1.15, CI=1.05 to 1.25) being more likely to be virally suppressed than patients receiving ART at a hospital level. However, patients receiving ART services at the CHC (aOR=1.14, CI=1.07 to 1.21) and PHC (aOR=1.51, CI=1.42 to 1.60) levels were also more likely to be LTFU than those who receive ART at a hospital level. The fixed effects model yielded the same results and are not reported here

Table 3: Logistic regression analysis (univariate) for current regimen and outcome variables

	VL suppression				LTFU			
Variable	Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio	p-value	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio	p-value
Current regimen								
First-line regimen	1	-			1			
Second-line regimen	0.37 (0.35-0.40)	**<0.001**	**0.26 (0.23-0.28)**	**<0.001**	0.82 (0.78-0.87)	**<0.001**	1.21 (1.09-1.35)	**<0.001**
Regimen combination								
d4t/3TC+EFV	1	-			1	-	1	
TDF/3TC/EFV	1.06 (0.97-1.16)	0.220	1.24 (1.10-1.40)	0.797	1.14 (1.09-1.19)	**<0.001**	0.14 (0.12-0.15)	**<0.001**
TDF/FTC/EFV (FDC)	0.83 (0.77-0.90)	**<0.001**	1.42 (1.26-1.59)	**<0.001**	0.83 (0.80-0.86)	**<0.001**	0.017 (0.015-0.019)	**<0.001**
Level of care								
Hospital	1				1		1	
CHC	1.91 (1.79-2.04)	**<0.001**	2.20 (2.02-2.39)	**<0.001**	1.27 (1.22-1.31)	**<0.001**	1.63 (1.55-1.71)	**<0.001**
PHC	1.22 (1.14-1.30)	**<0.001**	1.15 (1.05-1.25)	**0.001**	1.20 (1.16-1.25)	**<0.001**	1.77 (1.68-1.86)	**<0.001**

First-line treatment

Table 4 shows findings of univariate and multivariable logistic regression analyses of associations of demographic and clinical characteristics with VL suppression and LTFU for patients on first-line ART (the fixed effects model yielded the same results and are not reported here). Patients aged 25–34 years (aOR=1.89, CI=1.64 to 2.17), 35–49 years (aOR=3.00, CI=2.61 to 3.44) and 50+ years (aOR=4.50, CI=3.83 to 5.29) were all more likely to attain VL suppression than patients younger than 25 years. Patients with their most recent CD4 cell count between 101–200 cells/μL (aOR=1.85, CI=1.70 to 2.02), 201–350 cells/μL (aOR=3.70, CI=3.41 to 4.01), 351–500 cells/μL (aOR=6.13, CI=5.58 to 6.74) and above 500 cells/μL (aOR=11.96, CI=10.80 to 13.24) were all more likely to have suppressed VL than patients with their most recent CD4 cell count less or equal to 100 cells/μL. Patients who were initiated on first-line ART between 2011–2014, ≤350 CD4 cell count period (aOR=1.24, CI=1.14 to 1.35), and 2015, ≤500 cell count period (aOR=1.38, CI=1.22 to 1.56), were more likely to achieve virological suppression than patients initiated between 2004 and 2010 (≤200 cells/μL period). Patients receiving first-line ART at CHC (aOR=2.67, CI=2.46 to 2.90) and PHC (aOR=1.43, CI=1.32 to 1.55) levels were more likely to achieve virological suppression than those receiving first-line ART at hospital level. Patients aged 25–34 years (aOR=0.80, CI=0.75 to 0.86), 35–49 years (aOR=0.46, CI=0.43 to 0.49) and 50+ years (aOR=0.40, CI=0.37 to 0.43) were less likely to be LTFU than patients<25 years. Patients with a most recent CD4 cell count between 101–200 cells/μL (aOR=0.79, CI=0.75 to 0.84), 201–350 cells/μL (aOR=0.62, CI=0.60 to 0.65), 351–500 cells/μL (aOR=0.51, CI=0.49 to 0.54) and above 500 cells/μL (aOR=0.43, CI=0.41 to 0.45) were less likely to be LTFU than patients with most recent CD4 cell count≤100 cells/μL. Patients who were initiated on first-line ART between 2011 and 2014 were more likely to be LTFU as compared with those initiated prior (aOR=1.14, CI=1.09 to 1.19). Patients who were initiated on first-line ART between 2016 and 2020 were less likely to be LTFU than those initiated prior to 2011 (aOR=0.63, CI=0.60 to 0.65). Patients receiving first-line ART from CHC (aOR=1.47, CI=1.40 to 1.54) and PHC (aOR=1.56, CI=1.49 to 1.64) levels were more likely to be LTFU than those at hospital level.

Table 4: Logistic regression analysis (univariate and multivariable analysis) for patients on first-line ART regimens

	VL suppression				LTFU			
Variable	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Current age								
<25 years	1	-	1	-	1	-	1	-
25-34 years	1.54(1.40-1.71)	**<0.001**	1.76(1.55-1.99)	**<0.001**	0.97(0.92-1.01)	0.196	0.79(0.73-0.85)	**<0.001**
35-49 years	2.25(2.05-2.48)	**<0.001**	2.56(2.27-2.90)	**<0.001**	0.71(0.67-0.74)	**<0.001**	0.55(0.51-0.59)	**<0.001**
50+ years	3.43(3.05-3.87)	**<0.001**	3.72(3.21-4.32)	**<0.001**	0.63(0.59-0.66)	**<0.001**	0.54(0.50-0.60)	**<0.001**
Sex								
Female	1	-	1	-	1	-	1	-
Male	0.91 (0.87-0.96)	**0.001**	1.06(1.00-1.13)	0.056	1.01(0.98-1.04)	0.478	1.02(0.98-1.07)	0.262
Total duration on ART								
<5 years	1	-	1	-	1	-	1	-
5-9 years	2.60 (2.44-2.77)	**<0.001**	2.98(2.73-3.25)	**<0.001**	0.20 (0.19-0.21)	**<0.001**	0.0014(0.0012-0.0016)	**<0.001**
≥10 years	2.90 (2.67-3.16)	**<0.001**	4.69(4.06-5.41)	**<0.001**	0.048 (0.045-0.052)	**<0.001**	0.0000039(0.0000030-0.0000050)	**<0.001**
Most recent CD4 cell count								
≤100 cells/µl	1	-	1	-	1	-	1	-
101-200 cells/µl	1.88(1.73-2.04)	**<0.001**	1.85(1.69-2.01)	**<0.001**	0.81(0.77-0.85)	**<0.001**	0.91(0.84-0.97)	**<0.001**
201-350 cells/µl	3.68(3.39-3.98)	**<0.001**	3.59(3.31-3.91)	**<0.001**	0.67(0.64-0.70)	**<0.001**	0.80(0.75-0.86)	**<0.001**
351-500 cells/µl	5.81(5.30-6.38)	**<0.001**	5.71(5.19-6.28)	**<0.001**	0.54(0.51-0.57)	**<0.001**	0.84(0.78-0.90)	**<0.001**
>500 cells/µl	10.33(9.36-11.40)	**<0.001**	10.69(9.64-11.85)	**<0.001**	0.46(0.44-0.49)	**<0.001**	0.80(0.75-0.86)	**<0.001**
Years of ART initiation								
2004-2010 (≤200 cells/µl period)	1		1		1		1	
2011-2014 (≤350 cells/µl period)	0.93 (0.86-1.00)	0.053	1.90(1.68-2.16)	**<0.001**	1.13 (1.09-1.17)	**<0.001**	0.0057 (0.0048-0.0069)	**<0.001**
2015 (≤500 cells/µl period)	0.94 (0.84-1.05)	0.257	2.24(1.92-2.60)	**<0.001**	1.01 (0.96-1.06)	0.645	0.0012 (0.0010-0.0015)	**<0.001**
2016-2020 (Universal test and treat period)	0.61 (0.57-0.65)	**<0.001**	2.99 (2.64-3.39)	**<0.001**	0.76 (0.74-0.79)	**<0.001**	0.000022 (0.000017-0.000028)	**<0.001**
Level of care								
Hospital	1		1		1		1	
CHC	1.99 (1.85-2.14)	**<0.001**	2.76 (2.54-3.01)	**<0.001**	1.30 (1.25-1.35)	**<0.001**	1.53 (1.43-1.64)	**<0.001**
PHC	1.13 (1.05-1.21)	**0.001**	1.40 (1.29-1.51)	**<0.001**	1.22 (1.18-1.26)	**<0.001**	1.75 (1.63-1.88)	**<0.001**

Abbreviations: VL, viral load; LTFU, lost to follow-up; CI, confidence interval; p-value, significance; ART, antiretroviral therapy. **Bold p-values denote statistical significance at the *p≤ 0.05* level.**

Second-line treatment

Table 5 shows findings of univariate and multivariable logistic regression analyses of associations of demographic and clinical characteristics with VL suppression and LTFU for patients on second-line ART (the fixed effects model yielded the same results and are not reported here). Patients aged 25 years and older (25–34 years: aOR=2.01, CI=1.40 to 2.89, 35–49 years: aOR=3.13, CI=2.26 to 4.32 and 50+ years: aOR=3.91, CI=2.72 to 5.62) were more likely to be virally suppressed than patients younger than 25 years. Patients with recorded most recent CD4 cell counts of 101–200 cells/µL (aOR=1.28, CI=1.02 to 1.59), 201–350 cells/µL (aOR=2.19, CI=1.77 to 2.71), 351–500 cells/µL (aOR=4.13, CI=3.21 to 5.32) and above 500 cells/µL (aOR=8.32, CI=6.33 to 10.93) were more likely to achieve VL suppression than patients whose most recent CD4 cell count was ≤100 cells/µL. Patients who were initiated on second-line ART between 2011 and 2014 (aOR=1.20, CI=1.01 to 1.44) were more likely to achieve virological suppression than patients initiated between 2004 and 2010. Receiving second-line ART from a PHC (aOR=0.73, CI=0.57 to 0.94) was associated with virological failure in comparison to receiving second-line ART at a hospital level. Patients who received second-line ART at a CHC level were more likely to achieve virological suppression (aOR=1.32, CI=1.11 to 1.57). Unlike patients on first-line ART, patients on second-line ART aged 25–34 years (aOR=1.99, CI=1.36 to 2.91) and 35–49 years (aOR=1.46, CI=1.03 to 2.08) were more likely to be LTFU than patients<25 years. Patients with a most recent CD4 cell count 201–350 cells/ µL (aOR=0.70, CI=0.57 to 0.85), 351–500 cells/µL (aOR=0.70, CI=0.57 to 0.86) and 500 cells/µL (aOR=0.44, CI=0.36 to 0.54) were all less likely to be LTFU than patients with a most recent CD4 cell count≤100 cells/µL. Patients who were initiated on second-line ART between 2011–2014 (aOR=0.81, CI=0.70 to 0.93), 2015 (aOR=0.62, CI=0.46 to 0.85) and 2016–2020 (aOR=0.42, CI=0.33 to 0.52) were all less likely to be LTFU than those who were initiated between 2004 and 2010.

Table 5: Logistic regression analysis (univariate and multivariable analysis) for patients on second-line ART regimens.

	VL suppression				LTFU			
Variable	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p--value	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Current age								
<25 years	1	-	1	-	1	-	1	-
25-34 years	1.72(1.30-2.29)	**<0.001**	2.21(1.53-3.17)	**<0.001**	1.57(1.17-2.10)	**0.003**	1.22(0.73-2.04)	0.445
35-49 years	2.73(2.13-3.50)	**<0.001**	3.32(2.40-4.58)	**<0.001**	1.30(1.00-1.69)	0.054	1.01(0.63-1.62)	0.959
50+ years	3.52(2.63-4.70)	**<0.001**	3.92(2.72-5.64)	**<0.001**	1.02(0.76-1.36)	0.888	0.80(0.48-1.35)	0.408
Sex								
Female	1	-	1	-	1	-	1	-
Male	0.90(0.78-1.03)	0.135	1.04(0.89-1.25)	0.618	0.87(0.78-0.99)	**0.027**	0.85(0.69-1.05)	0.125
Total duration on ART								
<5 years	1	-	1	-	1	-	1	-
5-9 years	2.08(1.76-2.45)	**<0.001**	2.92(2.32-3.68)	**<0.001**	0.36(0.31-0.41)	**<0.001**	0.0030(0.0015-0.0062)	**<0.001**
≥10 years	3.14(2.64-3.75)	**<0.001**	6.80(5.14-9.00)	**<0.001**	0.063(0.052-0.077)	**<0.001**	0.0000082(0.0000033-0.000021)	**<0.001**
Most recent CD4 cell count								
≤100 cells/µl	1	-	1	-	1	-	1	-
101-200 cells/µl	1.37(1.10-1.70)	**0.004**	1.30(1.04-1.64)	**0.023**	1.01(0.82-1.24)	0.923	0.99(0.72-1.36)	0.941
201-350 cells/µl	2.27(1.85-2.80)	**<0.001**	2.16(1.73-2.70)	**<0.001**	0.78(0.64-0.94)	**0.011**	0.67(0.49-0.92)	**0.012**
351-500 cells/µl	4.17(3.27-5.33)	**<0.001**	4.11(3.17-5.34)	**<0.001**	0.82(0.67-1.01)	0.059	0.89(0.64-1.22)	0.455
>500 cells/µl	8.23(6.33-10.71)	**<0.001**	7.32(5.55-9.66)	**<0.001**	0.53(0.44-0.64)	**<0.001**	0.77(0.57-1.05)	0.099
Years of ART initiation								
2004-2010 (≤200 cells/µl period)	1				1		1	
2011-2014 (≤350 cells/µl period)	0.89 (0.76-1.04)	0.148	2.27(1.78-2.89)	**<0.001**	0.90 (0.79-1.03)	**0.126**	0.0057 (0.0033-0.0099)	**<0.001**
2015 (≤500 cells/µl period)	0.79 (0.58-1.07)	0.127	2.62(1.78-3.87)	**<0.001**	0.71 (0.54-0.95)	**0.019**	0.00072 (0.00028-0.0018)	**<0.001**
2016-2020 (Universal test and treat period)	0.73 (0.60-0.89)	**0.002**	4.96(3.63-6.79)	**<0.001**	0.52 (043-0.63)	**<0.001**	0.000023 (0.0000093-0.000058)	**<0.001**
Level of care								
Hospital	1				1		1	
CHC	1.18 (1.01-1.37)	**<0.001**	1.40 (1.18-1.68)	**<0.001**	0.88 (0.78-1.00)	0.054	0.69(0.55-0.85)	**0.001**
PHC	0.67 (0.54-0.84)	**<0.001**	0.69 (0.54-0.89)	**0.004**	0.80 (0.66-0.99)	**0.035**	0.82 (0.60-1.13)	0.225

Abbreviations: VL, viral load; LTFU, lost to follow-up; CI, confidence interval; p-value, significance; ART, antiretroviral therapy. **Bold p-values denote statistical significance at the *p≤ 0.05* level.**

DISCUSSION

This is one of the largest studies to date from the South African national HIV treatment programme reporting on ART uptake, virologic failure and retention in care. In this cohort, most patients did well virologically but retention in care was poor. The outcomes observed in this study are similar to those of other studies in sub-Saharan African countries [25-27], but different to most findings from high-income countries [5].

Various studies have reported improved treatment outcomes and retention in care associated with FDC, also noting that the improvement extends beyond the single pill versus multi-pill ART comparison to availability of adherence support, time between medical visits and patient waiting times [28,29]. In our analyses, patients on FDC were similarly more likely to achieve virological suppression and less likely to be LTFU. The simultaneous introduction of FDC and improvements in adherence interventions may have facilitated the improvement treatment outcomes and decline of LTFU between 2013 and 2019 [29].

Since the substitution of EFV with DTG, as of September 2019, less than 1500 patients were either initiated or switched to a DTG containing regimen by the end of February 2020. This accounted for 1% of the study cohort who were initiated or switched to DTG-based regimen in less than 6 months (between September 2019 and February 2020). The transition to a DTG-based regimen in South Africa is being done in a phased approach, and numbers of patients initiating DTG are expected to increase in subsequent years. Although the efficacy of DTG has been documented through clinical trials [30,31], the clinical benefits in this population are yet to be reported.

There was a correlation between level of care (facility type) and outcome variables (VL and LTFU). Expectedly, patients receiving ART services from the CHC and PHCs were more likely to achieve virological suppression but were also more likely to be LTFU than patients receiving ART services from the hospital level. Patients with HIV-related complications and other comorbidities are likely to have poorer outcomes [32,33] and are more often likely to receive ART services at hospital level [33]. Therefore, differences in outcomes between facilities (CHC and PHCs vs hospitals) may be partially attributable to these confounders. Additionally, favourable outcome in terms of virological suppression at PHC level when compared with hospitals could also be a demonstration of effective task shifting and decentralisation of services between primary and higher levels of care (secondary and tertiary) as well as out of the facility setting (eg, PHCs and CHCs run adherence clubs for stable, adherent ART patients) [10]. These levels of care could be used to provide models to improve virological suppression and adherence to treatment for hospitals as well.

With respect to first-line regimens, patients who were 25 years and older, patients with a most recent CD4 cell count above 100 cells/μL and patients who were initiated from 2011 onwards were all more likely to achieve VL suppression and remain in care. Since 2011, the South African ART programme has seen improvements in ART regimens (eg, changes from triple therapy to FDC in 2013) and CD4 cell count thresholds (eg, changes from 350 to 500 cells/μL in 2015) which has most likely attributed to better clinical outcomes [2]. These findings are consistent with the other studies which reported older patients who had higher CD4 cell counts and/ or initiated from 2011 onwards being more likely to obtain VL suppression and also remain in care [25-27,34-36].

Therefore, patients under 25 years, patients with a low CD4 cell count and those who were initiated between 2004 and 2010 need to be prioritised for interventions addressing treatment and adherence. Younger patients and low CD4 cell count have been previously noted for targeting in HIV treatment programme strengthening [25-27,34-36], and our analyses reinforces that these population groups remain at higher risk of less favourable treatment outcomes.

For patients on second-line regimens, higher CD4 cell count and patients who were initiated in 2011 onwards also predicted viral suppression and retention in care, as among patients on first-line treatment. However, being older predicted poor retention in care for patients on second-line ART, a finding that is inconsistent with previous findings from the same setting [10]. Furthermore, and similar to patients on first-line treatment, patients on second-line ART who were initiated from 2011 onwards were less likely to be LTFU. These findings corroborate other studies conducted in South Africa [28,29], and emphasise the importance of continuous improvement in ART service delivery, including implementation of appropriate adherence support mechanisms for medication and clinic visits and optimised treatment regimens.

Survival analysis demonstrated an immediate sharp decrease in retention in care for patients on first-line ART and started plateauing at year 5, while for patients on second-line ART, retention decreased steadily with increased time on ART. Early after ART initiation there are more transfers out, deaths and loss from care than at the point of switch to second-line, however after 15 years the proportions even out. Furthermore, decrease in retention in 2007–2011 period corresponds to a time of increasing ART decentralisation. Our finding suggests a need to engage patients throughout their treatment journey by possibly providing regular adherence counselling and community-based interventions such as adherence clubs [37,38]. These treatment adherence strategies have already been noted to yield good retention and clinical outcomes in many first-line ART cohorts in lower-middle-income countries [39,40].

VL suppression reduces the risk of HIV onward transmission and indicates good clinical outcomes and treatment adherence [10,41,42]. Overall, the high rates (91%) of VL suppression found in our study cohort is in keeping with the 90–90–90 UNAIDS targets, which includes making sure that 90% of all patients taking ART have suppressed VLs [43,44]. This suggests that prioritising interventions to promote adherence and VL monitoring in patients receiving ART has likely resulted in VL improvements. In contrast, we report higher LTFU up rates (32%) for the entire study cohort than previously reported in the Johannesburg inner city (region F) (between 10% and 20%) [10,29]. A study conducted in South Africa reported approximately up to 40% being LTFU within the first year of starting ART [45]. With the current recording systems, true LTFU cannot be measured and until South Africa employs a unique identifier system, the HIV programme will not be able to accurately report on people lost to the programme as opposed to stopping treatment at one facility and starting at another (without following the transfer processes).

Overall, findings regarding predictors of VL and LTFU for both regimens underscore the need to strengthen, possibly combined, strategies to not only promote adherence to ART but also to ensure that patients are retained in HIV care [10,37]. Effective strategies to improve adherence among patients on ART comprise intensive and targeted adherence counselling and sending treatment reminders [10,37,45]. Recommendations from patients attending ART clinics in the Johannesburg inner city (region F) include reducing the pill size, education on the benefits of taking ART and making injectable ART available [46,47]. As the duration between clinic visits can span up to 6 months, it is also crucial to consider approaches to enable continued patient-provider engagement between these visits to promote retention, for instance, regular provision of health gamification and videos/health resources using mHealth platforms [48,49].

Our study has some limitations. The analyses were completed for only 7 of over 120 health facilities in one South African metropolitan municipality, and findings may not be generalisable to other municipalities and districts in South Africa or to other country settings. Furthermore, although the department of health tries to ensure good quality of data in Tier.Net, we did encounter quality issues. In particular, due to data inconsistencies and missing information (TIER.Net only records the most recent VL count which overrides the previously captured value), we could not accurately calculate time to VL suppression or failure with only one VL reading available. A standard VL result of 124 copies/mL is captured in TIER.Net for patients whose laboratory results are reported as lower than detectable level. This makes it difficult to differentiate between patients who had an absolute value of VL results as ‘124’ and those who had VL results as ‘lower than detectable level’. This affects the calculated VL values such as the exact average VL count for the cohort. TIER.Net does not enable linking records between health facilities which results in a lack of documentation of a large proportion of transfers. It is plausible that this limitation in data increased during the 16-year study window as more facilities offering ART services became available for patients to transfer between. Deaths and

LTFU are poorly recorded on TIER.Net, therefore, it is possible that death and LTFU rates are generally higher than reported in this study. While the LTFU has increased and a lot of patients who missed their appointments were regarded as LTFU after 90 days without medication, it is possible that some of these patients regarded as LTFU are in fact receiving healthcare services at other facilities (self-transfer out) [5]. The association between lower CD4 count and increased LTFU could possibly be explained as the lower CD4 count (and accompanying poor health) resulted in unrecorded deaths subsequently contributing to the increased LTFU. Lastly, filing systems for paper-based records in many public health facilities in the study setting are inadequate. Therefore, it is possible that some files were misplaced or not available for back capture. However, to maximise the captured records, information was captured from patient files and the ART longitudinal paper-based register which was used in the public health setting before the TIER.Net electronic version was implemented.

CONCLUSION

While national ART guidelines and efforts to initiate people with HIV on treatment have contributed to a higher uptake of ART over time, much still needs to be done to improve retention in care; mostly in patients on a first-line regimen, and clinical outcomes; mostly in patients on a second-line regimen. Younger patients, patients with low CD4 cell counts and patients who were initiated on ART between 2004 and 2010 all showed poorer clinical and retention outcomes. Although slight efforts have been made to address similar findings, these demographic and clinical characteristics must be considered when designing/implementing treatment support strategies and models to improve retention in care. Support strategies could include directed patient management from the commencement of ART, community-based interventions, such as adherence clubs and ART pick-up points, or using digital health technology innovations for patient engagement between clinic visits, appointment and medication reminders and education.

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CHAPTER 4

Descriptive analysis of World Health Organization-recommended second-line antiretroviral treatment: A retrospective cohort data analysis

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ABSTRACT

Background. World Health Organization guidelines recommend that HIV patients who do not achieve viral suppression on efavirenz-based first-line antiretroviral therapy (ART) should be changed to a protease inhibitor (PI)-based regimen. In South Africa (SA), ~200 000 people are on second-line treatment, but little is known about these patients.

Objectives. To describe second-line black African patients in a large urban area.

Methods. A quantitative retrospective study of 825 second-line patients in central Johannesburg, SA (subdistrict F), was performed with data extracted from government databases. Demographic characteristics, treatment status and laboratory information were gathered, then analysed with CD4+ cell count, viral load (VL) and retention-in-care data as outcome variables.

Results. The average recorded time to VL measurement after the switch to a PI-based ART regimen was 20 months, and 83.1% (570/686) of patients with a recent VL achieved viral suppression while on second-line treatment. The most recent median CD4+ cell count for the cohort was 286 cells/µL (interquartile range 160 - 478), which represented a 177 cells/µL increase from the baseline count at the start of first-line ART. Slightly less than three-quarters (72.4%) of the population remained active in care in the study clinics from initiation on first-line ART. Demographic characteristics such as being <25 years of age, male sex and geographical transfer (started initial treatment in a different region) independently predicted low CD4+ cell counts and virological failure on second-line treatment. Patients with virological failure were most likely (odds ratio (OR) 3.13, 95% confidence interval (CI) 1.50 - 6.56) to be lost to follow-up after the switch, while patients from Hillbrow Community Health Centre (OR 0.27, 95% CI 0.16 - 0.44), South Rand Hospital (OR 0.24, 95% CI 0.12 - 0.47) and Jeppe Clinic (OR 0.38, 95% CI 0.16 - 0.88), three larger sites, were most likely to remain active in care.

Conclusions. VL suppression was high in patients on second-line treatment, but one-fifth of patients were lost to follow-up. Younger age, male sex and transfer from other treatment sites predicted poor treatment outcomes, highlighting opportunities for prioritisation of adherence interventions.

INTRODUCTION

South Africa (SA) has the world's highest HIV burden, with 7.52 million people (13.1% of the world's HIV population) living with HIV. However, AIDS-related deaths and new HIV infections have both been reduced by approximately half since 2004 [1]. A national antiretroviral therapy (ART) programme provides free medication to ~4.4 million people living with HIV [2]. The goals of ART are to prolong life expectancy, decrease opportunistic illnesses and improve quality of life, while also preventing transmission of the virus. These goals are achieved by suppressing the HIV viral load (VL), allowing restoration of immune function, as measured partly by increasing CD4+ cell counts [3,4].

Since 2012, all HIV-positive patients in SA have commenced treatment with a preferred first-line fixed-dose combination regimen of efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) [5-7]. This treatment regimen is favoured because of its tolerability, simplicity and cost-effectiveness, but it provides a low barrier for resistance, which results in treatment failure for a proportion of patients [8]. Patients who experience virological failure (VL ≥1 000 copies/mL) on at least two occasions 2 months apart are offered second-line treatment containing protease inhibitors (PIs), in accordance with local guidelines [7]. Although the exact transfer rates are unknown, it is estimated that there are almost 200 000 second-line patients in SA [5,9].

This progression from first- to second-line treatment is in accordance with World Health Organization (WHO) guidelines [10]. Up to 30% of second-line patients still experience virological failure in some SA cohorts [11]. Second-line treatment is complex, involving numerous tablets with substantial toxicity and twice-daily dosing. However, there are limited studies that explore second-line treatment outcomes [8,12,13]. Little is known about the long-term clinical outcomes of second-line patients. This study followed a large second-line cohort in Johannesburg, while also identifying demographic characteristics and laboratory and clinical factors that predict virological failure, which may allow for future targeted adherence and support interventions.

METHODS

Study design

This retrospective cohort study used the TIER.Net database for secondary data on adult second-line patients. TIER.Net is the ART monitoring and evaluation system used by the SA National Department of Health for recording HIV, pre-ART, ART and tuberculosis (TB) patient-level information including HIV diagnosis dates, HIV results, ART start dates, ART switch dates, HIV/TB co-infection, treatment retention, VL and CD4+ cell count results. Second-line patients were defined as patients who experienced virological failure (VL ≥1 000 copies/mL) on at least two occasions 2 months apart and were then switched to a PI-based regimen.

Setting

Records were reviewed for all ART patients from eight public health facilities in central Johannesburg (subdistrict F). The facilities were two hospitals, one community health centre (CHC) and five primary healthcare clinics.

Data collection

The total cohort of 825 represented all patients from the facilities who initiated their second-line treatment between 1 January 2014 and 31 December 2015. This cut-off period was chosen to give the cohort patients a minimum of 1 year to receive their annual standard-of-care VL test. In order to isolate this cohort, data were extracted from the TIER.Net database for all patients active on ART (*N*=56 894). A total of 53 287 patients on first-line treatment were then excluded, leaving a total of 3 607 active patients on second-line treatment. Of these second-line patients, 2 781 were excluded because they initiated their second-line treatment before 1 January 2014. Of the remaining 826 patients who met the inclusion criteria, one had missing information and was omitted, and the remaining 825 were followed until data collection ended in July 2017. The participant flow diagram is shown in Fig. 1.

All data were exported from TIER.Net to Excel 2016 Professional Plus (Microsoft, USA), where data were cleaned and formatted. The following variables were extracted for further analysis: treatment facility, gender, date of birth, age at ART switch, ART start date, second-line treatment start date, baseline ART regimen, baseline CD4+ cell count at start of ART, most recent CD4+ cell count (after ART switch), most recent VL (after ART switch), and retention-in-care status.

CD4+ cell counts were presented in four ranges for values ≤500 cells/μL and as a single category for all values >500 cells/μL. Since this cohort started ART before 2017, the CD4+ cell count disaggregation reported here was guided by the WHO guidelines [14-16]. VL was categorised into suppressed or unsuppressed based on the WHO threshold for suppression of <1 000 copies/mL [7,17]. Retention-in-care status was assessed as at 31 July 2017, and categorised into active in care (AIC), lost to follow-up (LTFU), transferred out (moved outside a facility included in the analysis), or known to be dead.

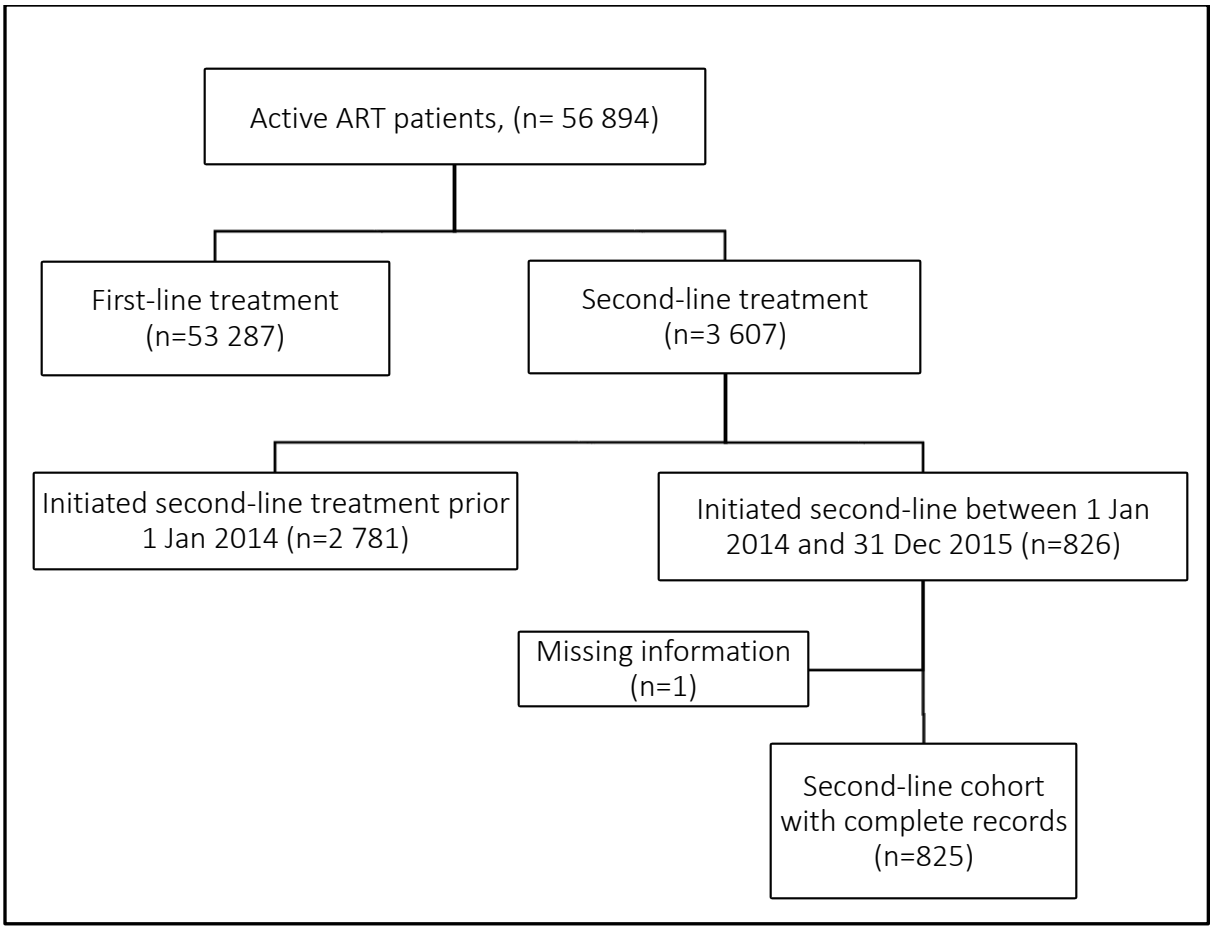

Figure 1 Second-line cohort flow diagram. (ART = antiretroviral therapy)

Data analysis

Data from the Excel spreadsheets were exported to Stata version 15.1 (StataCorp, USA) for analysis. Continuous data were summarised using medians (and interquartile ranges where appropriate) and then grouped into categories to define demographic characteristics. Three outcome variables, CD4+ cell count levels, VL and retention-in-care status, were quantified at the cohort level, then analysed further to identify associations between outcome variables and selected demographic characteristics with Pearson's $\chi 2$ tests. Furthermore, multiple logistic regression models were built for the outcome variables to identify independent predictors. These predictors were reported as unadjusted and adjusted odds ratios (ORs), with 95% confidence intervals (CIs) and *p*-values; $p<0.05$ was considered significant. Survival analysis (for the LTFU category) was conducted using the Kaplan- Meier estimator to understand the pattern of attrition.

Ethical considerations

Ethical clearance was received from the University of the Witwatersrand Human Research Ethics Committee (ref. no. M170691). In addition, approval was granted by the Johannesburg Health District (ref. no. 2017-08-003) and the National Health Research Database (ref. no. GP_201708_030).

RESULTS

Demographic profile (Table 1)

At the start of first-line ART, the cohort had an average baseline CD4+ count of 109 cells/µL, and 59.9% of the patients were female. The median age at the start of second-line treatment was 37 years, the median duration of first-line ART was 63 months, and patients switched from first-line to second-line treatment after 38 months on average. Zidovudine/ lamivudine/lopinavir/ritonavir (AZT/3TC/ LPV/r) was the most common second-line antiretroviral, with 68.0% of the cohort on this combination. The other 32.0% were on tenofovir/lamivudine/lopinavir/ritonavir (TDF/3TC/LPV/r).

For the cohort, a single site (Hillbrow CHC) provided 352 (42.7%) of patients, while Charlotte Maxeke Johannesburg Academic Hospital, South Rand Hospital and Yeoville Clinic were the only other facilities that provided more than 100 patients. Just under half of the patients had been transferred to their current treatment facilities from outside subdistrict F, while the other 56.9% were new patients who had commenced treatment in subdistrict F.

Table 1. Demographic characteristics

Characteristic	Median	Inter-quartile range
Age at start of second-line treatment (N=825)	37 years	33-43 years
Duration on ART since first-line treatment (N=825)	63 months	25-94 months
Time to switch from first to second-line treatment (N=745)	38 months	19-67 months
Baseline CD4 cell count at start of ART (N=705)	109 cells/ul	42-204 cells/ul
Characteristic	**Frequency**	**Percentage**
Facility (N=825)		
80 Albert Street Clinic	18	2.2
Charlotte Maxeke Hospital	116	14.1
Hillbrow CHC	352	42.7
Jeppe Clinic	47	5.7
Joubert Park Clinic	30	3.6
Malvern Clinic	16	1.9
Rosettenville Clinic	10	1.2
South Rand Hospital	122	14.8
Yeoville Clinic	114	13.8
Age at ART switch (N=825)		
<25 years	25	3.0
25-34 years	251	30.4
35-49 years	466	56.5
50+ years	83	10.1
Gender (N=825)		
Female	494	59.9
Male	331	40.1
New patients and transfers in (N=825)		
New patients	470	57.0
Transfer-in patients	355	43.0
Total duration on ART (N=825)		
1-4 years	247	29.9
5-9 years	474	57.5
≥10 years	104	12.6
Prescribed second-line treatment (N=825)		
TDF/3TC/LPV/r	264	32.0
AZT/3TC/LPV/r	561	68.0
Baseline CD4 cell count at start of ART (N=705)		
<100 cells/ul	330	46.9
101-200 cells/ul	192	27.2
201-350 cells/ul	127	18.0
351-500 cells/ul	34	4.8
>500 cells/ul	22	3.1

Abbreviations: N, number; IQR, interquartile range; ART, antiretroviral therapy; CHC, community health centre; TDF/3TC/LPV/r, tenofovir/lamivudine/lopinavir/ritonavir; AZT/3TC/LPV/r, zidovudine/lamivudine/lopinavir/ritonavir.

Outcome variables

A summary of the cohort outcome variables is set out in Table 2. In order to evaluate predictors for the three outcome variables, CD4+ cell count, VL and retention-in-care status, correlations were explored with different demographic characteristics.

Table 2. Outcome variables

Outcome Variables	Median	Inter-quartile range
Most recent CD4 cell count	286 cells/ul	160-478 cells/ul
Most recent viral load	124 copies/ml	46-639 copies/ml
<1000 copies/ml	124 copies/ml	28-124 copies/ml
≥1000 copies/ml	36 612 copies/ml	7563-167 110 copies/ml
Time to recorded viral load after ART switch	20 months	14-28 months
Characteristic	**Frequency**	**Percentage**
Most recent CD4 cell count (N=367)		
<100 cells/ul	60	16.4
101-200 cells/ul	58	15.8
201-350 cells/ul	85	23.2
351-500 cells/ul	73	19.9
>500 cells/ul	91	24.8
Most recent viral load (N=686)		
<1000 copies/ml	570	83.1
≥1000 copies/ml	116	16.9
Retention in care status (N=825)		
Active in care	597	72.4
LTFU	161	19.5
Transferred/moved out	59	7.2
Died	8	1.0

Abbreviations: N, number; IQR, interquartile range; VL, viral load; ART, antiretroviral therapy; AIC, active in care; LTFU, lost to follow-up.

Gender, new v. transferred-in patients, total duration of ART, second-line regimen, baseline CD4+ cell count at ART start and most recent VL were all correlated with the CD4+ cell count outcome. Age at ART switch, gender, new v. transferred-in patients (patients who were now on second-line treatment in subdistrict F but started their initial treatment in a different region) and most recent CD4+ cell count were all correlated with VL outcomes, while facility, duration of ART, baseline CD4+ cell count at start of ART and most recent VL were all significantly correlated with retention-in-care status outcomes. The Pearson's $\chi 2$ values are presented in Table 3, and to ensure that there were no affirmative confounders, all variables underwent further logistical analysis with ORs and adjusted ORs. One affirmative confounder was identified (age at ART switch and retention-in-care status) and added to the statistically significant correlations, which are presented in Table 4.

Table 3. Correlations between outcome variables and demographic characteristics

	Most recent CD4 cell count (cells/ ul)			Most recent viral load (copies/ml)			Retention in care status		
	≤500 (%)	>500 (%)	P-value (n)	<1000 (%)	≥1000 (%)	P-value (n)	AIC	LTFU	P-value (n)
Age at ART switch									
<25 years	72.7	27.3		57.9	42.1		63.6	36.4	
25-34 years	80.0	20.0	0.147	82.2	17.8	**0.020**	77.1	22.9	0.180
35-49 years	75.3	24.7	(367)	84.0	16.0	(686)	79.5	20.5	(758)
50+ years	61.5	38.5		87.3	12.7		84.2	15.8	
Gender									
Female	70.4	29.6	**0.013**	86.7	13.3	**0.002**	80.4	19.6	0.366
Male	81.8	18.2	(367)	77.9	22.1	(686)	77.7	22.4	(758)
Facility									
80 Albert Street Clinic	71.4	28.6		86.7	13.3		86.2	13.9	
Charlotte Maxeke Hospital	74.0	26.0		79.8	20.2		100.0	0.0	
Hillbrow CHC	74.8	25.2		85.9	14.1		63.4	36.6	
Jeppe Clinic	66.7	33.3	0.758	86.1	13.9	0.776	81.8	18.2	**<0.001**
Joubert Park Clinic	81.3	18.7	(367)	82.6	17.4	(683)	64.3	35.7	(770)
Malvern Clinic	62.5	37.5		87.5	12.5		87.5	12.5	
Rosettenville Clinic	50.0	50.0		85.7	14.3		57.1	42.9	
South Rand Hospital	78.5	21.5		78.4	21.6		87.5	12.5	
Yeoville Clinic	79.2	20.8		82.1	17.8		61.2	38.8	
New patients or transfers-in									
New patients	79.2	20.8	**0.013**	80.1	19.9	**0.010**	77.0	23.0	0.169
Transfer-in patients	67.5	32.5	(367)	87.5	12.5	(683)	81.1	18.9	(758)
Total duration on ART									
1-4 years	80.8	19.2		80.2	19.8		68.5	31.5	
5-9 years	74.9	25.1	**0.007**	82.8	17.2	0.140	83.3	16.7	**<0.001**
≥10 years	56.4	43.6	(367)	89.6	10.4	(684)	81.6	18.4	(758)
Prescribed second-line treatment									
TDF/3TC/LPV/r	63.5	36.5	**<0.001**	84.6	15.4	0.461	76.8	23.2	0.359
AZT/3TC/LPV/r	80.6	19.4	(367)	82.4	17.6	(686)	79.7	20.3	(758)
Baseline CD4 cell at start of ART									
<100 cells/ul	84.2	15.8		85.0	15.0		80.1	19.9	
101-200 cells/ul	75.9	24.1	**0.001**	80.2	19.8	0.333	82.5	17.5	**0.005**
201-350 cells/ul	75.0	25.0	(367)	78.4	21.6	(585)	78.2	21.9	(647)
351-500 cells/ul	64.0	36.0		91.3	8.7		51.7	48.3	
>500 cells/ul	58.5	41.5		87.5	12.5		79.0	21.0	
Most recent CD4 cell count									
<100 cells/ul	-	-	-	72.9	27.1	**<0.001**	70.0	30.0	0.102

101-200 cells/ul	-	-		76.0	24.0	(327)	82.7	17.3	(337)
201-350 cells/ul	-	-		68.8	31.2		78.5	21.5	
351-500 cells/ul	-	-		85.5	14.5		82.6	17.4	
>500 cells/ul	-	-		95.4	4.6		88.5	11.5	
Most recent viral load									
<1000 copies/ml	68.6	31.4	**<0.001**	-	-	-	89.1	10.9	**<0.001**
≥1000 copies/ml	93.6	6.4	(327)	-	-		59.8	40.2	(711)

Abbreviations: n, number; VL, viral load; AIC, active in care; LTFU, lost to follow-up; CHC, community health centre; ART, antiretroviral therapy; TDF/3TC/LPV/r, tenofovir/lamivudine/lopinavir/ritonavir; AZT/3TC/LPV/r, zidovudine/lamivudine/lopinavir/ritonavir. **Bold indicates significant values at $p<0.05$.**

Table 4. Logistical analysis of second-line patients for CD4 cell count, VL and LTFU

Demographic Variable	Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Most recent CD4 cell count > 500 cells/ul				
Gender				
Female	1.0	-	1.0	-
Male	0.53 (0.32-0.88)	**0.013**	0.56 (0.33-0.98)	**0.043**
New patients or transfers-in				
New patients	1.0	-	1.0	-
Transfer-in patients	0.54 (0.33-0.88)	**0.014**	0.71 (0.41 -1.24)	0.229
Total duration on ART				
1-4 years	1.0	-	1.0	-
5-9 years	1.41 (0.82-2.40)	0.212	1.75 (0.96 -3.18)	0.066
≥10 years	3.23 (1.51-6.91)	**0.002**	2.72 (1.09-6.80)	**0.031**
Prescribed second-line treatment				
TDF/3TC/LPV/r	1.0	-	1.0	-
AZT/3TC/LPV/r	0.42 (0.26-0.69)	**0.001**	0.63 (0.35-1.13)	0.118
Baseline CD4 cell count at start of ART				
<100 cells/ul	1.0	-	1.0	-
101-200 cells/ul	1.69 (0.86-3.35)	0.130	1.46 (0.69-3.13)	0.322
201-350 cells/ul	1.78 (0.83-3.84)	0.141	2.05 (0.86-4.91)	0.106
351-500 cells/ul	3.01 (1.19-7.63)	**0.020**	4.09 (1.23-13.56)	**0.021**
>500 cells/ul	3.80 (1.96- 7.39)	**<0.001**	3.22 (1.53-6.78)	**0.002**
Most recent viral load				
<1000 copies/ml	1.0	-	1.0	-
≥1000 copies/ml	0.15 (0.052-0.42)	**<0.001**	0.16 (0.056-0.48)	**0.001**
Viral load suppression (≤1000 copies/ml)				
Age at ART switch				
<25 years	1.0	-	1.0	-
25-34 years	3.37 (1.26-8.98)	**0.015**	3.18 (0.69-14.55)	0.137
35-49 years	3.81 (1.47-9.84)	**0.006**	3.58 (0.81-15.82)	0.092
50+ years	5.01 (1.59-15.79)	**0.006**	3.87 (0.70-21.42)	0.121
Gender				
Female	1.0	-	1.0	-
Male	0.54 (0.36-0.81)	**0.003**	0.63 (0.35-1.12)	0.116
New patients or transfers-in				
New patients	1.0	-	1.0	-
Transfer-in patients	0.58 (0.38-0.89)	**0.013**	0.86 (0.45- 1.62)	0.635
Most recent CD4 cell count				
<100 cells/ul	1.0	-	1.0	-
101-200 cells/ul	1.17 (0.47-2.92)	0.726	1.13 (0.44-2.91)	0.792
201-350 cells/ul	0.82 (0.37-1.81)	0.618	0.76 (0.33-1.72)	0.508

351-500 cells/ul	2.18 (0.85-5.66)	0.107	1.98 (0.75-5.24)	0.169
>500 cells/ul	7.71 (2.34-25.29)	**0.001**	6.52 (1.94-21.85)	**0.004**
Retention in care status - LTFU				
Age at ART switch				
<25 years	1.0	-	1.0	-
25-34 years	0.57 (0.23-1.39)	0.216	0.53 (0.21-1.32)	0.175
35-49 years	0.49 (0.21-1.18)	0.114	0.48 (0.20-1.16)	0.103
50+ years	0.36 (0.13-1.02)	**0.053**	0.35 (0.12-1.01)	**0.053**
Facility				
80 Albert Street Clinic	Empty	-	Empty	-
Charlotte Maxeke Hospital	1.0	-	1.0	-
Hillbrow CHC	0.27 (0.16-0.44)	**<0.001**	0.15 (0.07-0.33)	**<0.001**
Jeppe Clinic	0.38 (0.16-0.88)	**0.024**	0.074 (0.009- 0.59)	**0.014**
Joubert Park Clinic	0.91 (0.39- 2.14)	0.837	0.73 (0.23- 2.35)	0.599
Malvern Clinic	0.26 (0.06- 1.21)	0.086	0.45 (.09- 2.32)	0.343
Rosettenville Clinic	0.78 (0.19-3.20)	0.734	0.82 (0.14-4.77)	0.826
South Rand Hospital	0.24 (0.12-0.47)	**<0.001**	0.25 (0.11-0.58)	**0.001**
Total duration on ART				
1-4 years	1.0	-	1.0	-
5-9 years	0.47 (0.32-0.68)	**<0.001**	1.11 (0.60-2.04)	0.744
≥10 years	0.54 (0.30-0.96)	**0.035**	1.13 (0.49-2.65)	0.765
Baseline CD4 cell count at start of ART				
<101 cells/ul	1.0	-	1.0	-
101-200 cells/ul	0.86 (0.54-1.39)	0.544	0.70 (0.33-1.50)	0.362
201-350 cells/ul	1.15 (0.69-1.93)	0.585	1.14 (0.53-2.44)	0.734
351-500 cells/ul	3.13 (1.50-6.56)	**0.002**	5.59 (1.89- 16.58)	**0.002**
>500 cells/ul	1.19 (0.73-1.94)	0.486	1.20 (0.59- 2.43)	0.613
Most recent viral load				
<1000 copies/ml	1.0	-	1.0	-
≥1000 copies/ml	3.63 (2.19-6.02)	**<0.001**	4.12 (2.32-7.29)	**<0.001**

Abbreviations: VL, viral load; LTFU, lost to follow-up; OR, odds ratio: CI, confidence interval; aOR, adjusted OR; ART, antiretroviral therapy; TDF/3TC/LPV/r, tenofovir/lamivudine/lopinavir/ ritonavir; AZT/3TC/LPV/r, zidovudine/lamivudine/lopinavir/ritonavir; VL, viral load; CHC, community health centre. **Bold values indicates significant values at $p<0.05$.**

CD4+ cell count

For the cohort, the most recent median CD4+ cell count was 286 cells/µL, which represented a 177 cells/µL (270%) increase from the 109 cells/µL baseline count at the start of ART. Of the patients, 132 (22.5%) achieved healthy CD4+ cell counts >500 cells/µL, whereas only 22 (3.1%) were above this threshold with their baseline CD4+ cell counts.

Males (OR 0.53, 95% CI 0.32 - 0.88) and patients transferred into their current ART facility (OR 0.54, 95% CI 0.33 - 0.88) were both less likely to have a CD4+ cell count >500 cells/µL at last measurement than females and new patients, respectively. Patients taking AZT/3TC/ LPV/r as their regimen were also less likely (OR 0.42, 95% CI 0.26 - 0.69) to have a CD4+ cell count >500 cells/µL than patients taking TDF/3TC/LPV/r. Patients who had been on ART for at least 10 years were more likely to achieve CD4+ cell counts >500 cells/µL than patients who had been on ART for ≤4 years, with an OR of 3.23 (95% CI 1.51 - 6.91). Patients with virological failure on second-line treatment (OR 0.15, 95% CI 0.052 - 0.42) were less likely to achieve CD4+ cell counts >500 cells/µL than virologically suppressed patients.

VL suppression

The average time (based on VL dates included in patient records) to VL measurement after ART switch was 20 months, and the most recent median VL was 124 copies/mL. A total of 570 patients (83.1%) achieved viral suppression based on the 1 000 copies/mL threshold.

VL suppression was less likely in male patients than in females (OR 0.54, 95% CI 0.36 - 0.81) and in patients transferred from ART facilities outside subdistrict F (OR 0.58, 95% CI 0.38 - 0.89). Suppression was also directly related to age at ART switch, with the oldest group (patients aged ≥50 years) far more likely to achieve viral suppression than the youngest group (<25 years) (OR 5.01, 95% CI 1.59 - 15.79).

Retention-in-care status

As a cohort, 597 patients (72.4%) remained AIC until data collection ended in July 2017. Of the outstanding patients, 161 (19.5%) were lost to follow-up, while 59 (7.2%) were transferred or moved out of subdistrict F, and 8 (1.0%) died. Total duration of ART was a significant predictor of retention-in-care status, as patients on ART for 5 - 9 years (OR 0.47, 95% CI 0.32 - 0.68) and >10 years (OR 0.54, 95% CI 0.30 - 0.96) were approximately twice as likely to remain AIC for the duration of the study as those on ART for <5 years. Age at ART switch showed that patients aged >50 years (OR 0.36, p=0.053) were most likely to be retained in care.

Three facilities, Hillbrow CHC (OR 0.27, 95% CI 0.16 - 0.44), Jeppe Clinic (OR 0.38, 95% CI 0.16 - 0.88) and South Rand Hospital (OR 0.24, 95% CI 0.12 - 0.47) were less likely than the others to have patients lost to follow-up. Patients with virological failure on second-line treatment were almost four times (OR 3.63, 95% CI 2.19 - 6.02) more likely to be lost to follow-up than virologically suppressed patients. Patients with baseline CD4+ cell counts between 351 and 500 cells/µL at the start of ART were three times (OR 3.13, 95% CI 1.50 - 6.56) more likely to be lost to follow-up than patients with a CD4+ cell count <101 cells/ µL. No other baseline CD4+ cell count categories or most recent CD4+ cell counts were significant predictors of retention-in-care status.

Survival analysis (Fig. 2) shows an expected decrease in patient retention in care. However, the drop becomes steadier from month 100 (just over 8 years on treatment) and declines sharply at month 150 (12.5 years on treatment).

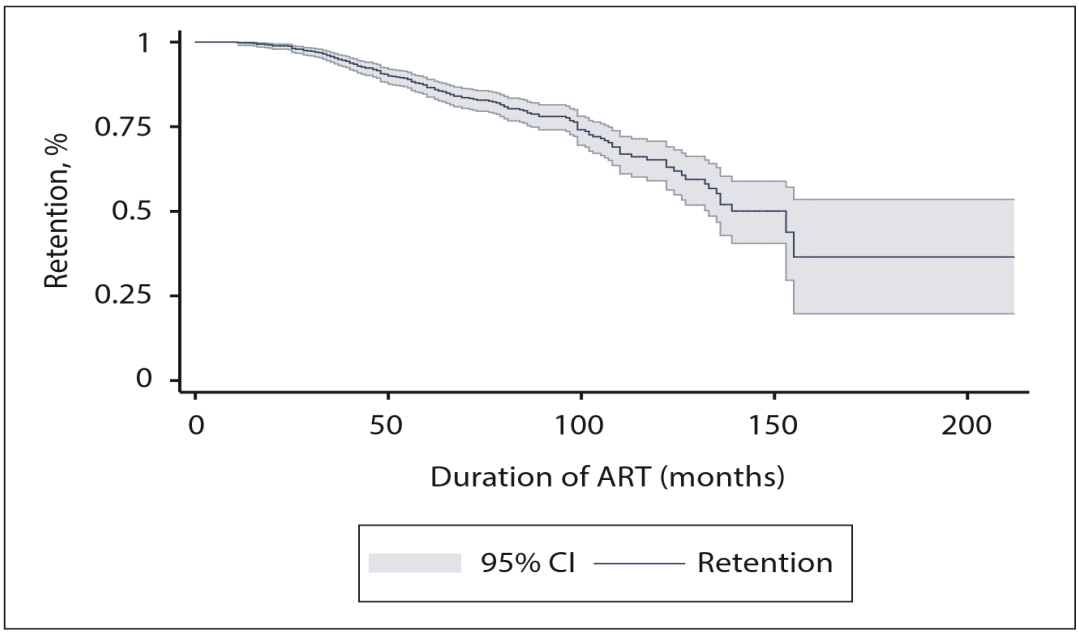

Figure 2 Retention-in-care estimates: loss to follow-up over time. (CI = confidence interval.)

DISCUSSION

Global intentions for successful scaling up of ART include ensuring that 90% of all patients receiving WHO-endorsed ART are retained in care with suppressed VLs [18]. Switching treatment-failing patients from first-line to second-line regimens has been policy in the SA public health setting since inception of the ART programme in 2004 [11]. However, not much has been done to describe the long-term clinical outcomes of second-line cohorts [19], particularly in this setting, highlighting the value of our findings. Patients starting second-line treatment tended to have low CD4+ cell counts, but 83.1% of our cohort showed viral suppression after switching from first-line treatment, demonstrating similar suppression rates to historical first-line treatment (85% suppression rate) in Johannesburg subdistrict F [20]. The low CD4+ cell counts despite viral suppression could be indicative of slow CD4+ cell count recovery [21]. Just under three-quarters (72.4%) of our patients remained in care in the study sites over the reported period. The remaining 27.6% were no longer receiving care at the study sites (i.e. transferred out), were lost to follow-up or died. This is slightly lower than the reported retention rate of 78% in a first-line treatment cohort from inner-city Johannesburg [22].

Recent VL suppression and recent CD4+ cell counts >500 cells/ µL were both correlated with a number of independent variables: males and transferred-in patients both had lower CD4+ cell counts and greater virological failure. Patients on TDF/3TC/LPV/r and patients with long durations of ART were correlated with CD4+ cell counts >500 cells/µL, but they did not show any statistically significant relationships with VL suppression. Age at ART switch did, however, show a strong stepwise correlation with virological failure, with patients aged 25-34 years, 35-50 years and >50 years each increasingly more likely to achieve viral suppression than patients aged <25 years. There was also a correlation between age at ART switch and retention-in-care status, as patients >50 years of age were more likely to remain AIC. This is in keeping with recent findings from Kenya that older ART patients were more likely to remain in care than younger patients [23], and older pooled Kenyan, Tanzania, Mozambican and Rwandan data [24]. Only three facilities, Hillbrow CHC, Jeppe Clinic and South Rand Hospital, were strongly associated with raised AIC rates. These findings are consistent with various reports released between 2014 and 2018 that described these three facilities, together with a few others in the Johannesburg metropolitan municipality, as providing high standards of care, their patients having comparatively short waiting times and good clinical support services (within facilities and from external health systems-strengthening support partners) in terms of implementation of clinical guidelines and leadership [25-27]. Ensuring quality of care, a sufficient space to provide ART services and shorter waiting times for ART patients have long been associated with patient retention and adherence to treatment [28,29]. Additionally, these findings demonstrate effective task shifting of ART services within the healthcare facilities and decentralisation of services between primary and higher levels of care (secondary and tertiary) [29-31], as well as out of the facility (e.g. Hillbrow CHC runs adherence clubs for stable, adherent ART patients). These three facilities could therefore be identified as providing models in terms of retention in care and adherence to treatment for other health facilities to follow.

Patients with baseline CD4+ cell counts at the start of ART of 351 - 500 cells/µL were approximately three times more likely to be lost to follow-up than patients with CD4+ cell counts ≤100 cells/µL. It could be assumed that since patients with low CD4+ cell counts are at an increased risk of opportunistic infections and other HIV-related complications, and of experiencing drug toxicity related to ART and HIV complications, they tend to remain in HIV care because they are ill and/or accessing care for multiple illnesses [32-34]. Patients who have been on ART for ≥5 years are ~50% less likely to be lost to follow-up than patients in their first 4 years of treatment. This evidence provides an opportunity for engaging patients from treatment initiation by providing additional support and counselling to ensure that they remain engaged throughout their treatment span. [35] Support and counselling benefits have been reported in first-line treatment cohorts where similar retention-in-care patterns were identified [35,36].

Mberi *et al*.[36] described a group receiving care from 2002 to 2012 at a high-volume SA ART clinic. They reported 40% of the patients being LTFU within 12 months of starting ART, a slight subsequent decrease in retention, a sharp decline from year 5, and plateauing at year 8. Our group displayed better long-term retention, with the initial sharp decline only being seen at year 8 and plateauing halfway through year 12. Patient and programme monitoring, actively implementing adherence and retention programmes, better-quality service delivery (described above) and possible improved accountability on the part of patients may have resulted in these slightly enhanced retention rates. The implication is that aggressively enforcing adherence and retention strategies will lead to better clinical outcomes and higher retention-in-care rates.

Study limitations

The analysis was performed for a limited number of facilities in one SA district and may not necessarily be generalisable to all the other districts. Owing to inconsistencies in data quality from TIER.Net it was difficult to accurately calculate time to second-line treatment from the exact time of treatment failure, as well as the time to suppression data. A standard VL result of 124 copies/mL is captured into TIER.Net for patients who have a laboratory result reported as lower than detectable level (instead of actual values). This affects the calculated median and interquartile range values.

CONCLUSION

Our study described the long-term clinical outcomes of second-line patients and identified demographic, laboratory and clinical factors that predicted virological failure in this group. The patients in this cohort did well virologically after switching to second-line therapy, although poorer outcomes remain an issue, especially among younger and male patients. The study also identified transfer of patients and patients on AZT/3TC/LPV/r as sub demographics that were likely to be associated with poorer laboratory outcomes. All these are easily identifiable factors that may trigger added adherence and support interventions including intensive patient engagement during the first few years of ART, targeted population-specific adherence support programmes, using mobile health solutions for patient communication and appointment reminders, prioritising male and youth-friendly ART adherence and retention initiatives, and implementing a single patient identifier to accurately monitor patient and programme outcomes.

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CHAPTER 5

Predictors of treatment adherence and virological failure among people living with HIV receiving antiretroviral therapy in a South African rural community: a sub-study of the ITREMA randomised clinical trial.

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ABSTRACT

A large proportion of people living with HIV (PLHIV) in sub-Saharan Africa reside in rural areas. Knowledge of enablers and barriers of adherence to antiretroviral treatment (ART) in these populations is limited. We conducted a cohort study of 501 adult PLHIV on ART at a rural South African treatment facility as a sub-study of a clinical trial (ClinicalTrials.gov NCT03357588). Socio-economic, psychosocial and behavioural characteristics were assessed as covariates of self-reported adherence difficulties, suboptimal pill count adherence and virological failure during 96 weeks of follow-up. Male gender was an independent risk factor for all outcomes. Food insecurity was associated with virological failure in males. Depressive symptoms were independently associated with virological failure in both males and females. Household income and task-oriented coping score were protective against suboptimal pill-count adherence. These results underscore the impact of low household income, food insecurity and depression on outcomes of ART in rural settings and confirm other previously described risk factors. Recognition of these factors and targeted adherence support strategies may improve patient health and treatment outcomes.

Key words: *antiretroviral therapy, adherence, pill count, virological failure, depression, South Africa*

INTRODUCTION

South Africa (SA) has an estimated HIV prevalence of 13.7%, with approximately 8.2 million people living with HIV (PLHIV) in 2021 [1]. Over one-third of the South African population resides in rural settings [2]. Rural populations are characterized by disadvantaged socio-economic status, limited access to healthcare services, and poor infrastructure and healthcare resources, when compared to their urban counterparts [3]. These factors adversely affect access and adherence to HIV treatment, potentially resulting in worse health outcomes for PLHIV [3,4].

Studies report episodes of ART non-adherence in around one-third of PLHIV residing in rural sub-Saharan Africa [4–7]. Non-adherence to ART in sub-Saharan Africa is associated with patient-related risk factors and social determinants, including changes in daily activities, forgetting to take ART, lack of health literacy, unwillingness to take ART, unemployment, poverty, HIV-status disclosure concern, HIV-related stigma, lack of clinician trust, poor coping mechanisms and mental health problems [8–11] The effect of these risk factors may be more profound in rural populations, as studies on barriers to care found that PLHIV in rural areas report more and more severe barriers to care than those living in urban areas [12,13]. This may be of particular relevance to male PLHIV in sub-Saharan African settings, who are at increased risk of various adverse outcomes of treatment, in part stemming from lack of access to care [14–16].

Suboptimal ART adherence can result in virological failure, which has adverse consequences for both individual and public health. Firstly, virological failure of ART is associated with an increased risk of disease progression and reduced survival [17,18]. Secondly, virological failure is often accompanied by the development of HIV drug resistance [19,20]. Drug resistance requires switching to more complex and expensive ART regimens, which have a higher pill burden, and often have less tolerable side effects [21,22]. Finally, virological failure greatly increases the risk of onward transmission of HIV [23].

As roll-out of ART continues to expand in South Africa, efforts are being made to optimize adherence to treatment and treatment efficacy. The recent adoption of dolutegravir (DTG) for all adult PLHIV is expected to improve adherence and efficacy [24]. Effective ART adherence support requires an understanding of the multi-level factors affecting overall adherence, which include socio-demographic, socio-economic, psycho-social and environmental conditions [25]. Knowledge of these factors may be used to identify individuals at risk of non-adherence and to identify factors that can promote ART adherence and improve patient care and programmatic outcomes. The aim of this study is to assess risk factors for adverse outcomes of ART, namely non-adherence and virological failure in rural South African PLHIV. This study also aims to describe the differential risk profiles associated with each of these outcomes.

METHODS

Design and Procedures

We conducted a prospective cohort study as a sub-study of the Intensified Treatment Monitoring Strategy to Prevent Accumulation of Drug Resistance (ITREMA; Clinicaltrials.gov NCT03357588). ITREMA was an open-label randomized clinical trial evaluating different treatment monitoring strategies for first-line ART, which ran from June 2015 to January 2019 [26]. In this trial, patients initiating ART were to be randomized after six months of ART and patients already on ART were randomized at 6 months after the last viral load measurement [26]. The trial protocol can be found in the Supplementary materials (Supplementary material 5).

Parent study control arm

Patients randomly assigned to this arm were monitored in full concordance with current South African NDoH guidelines in use at the study site. Viral load measurements were performed at month 12 and 24 after start of ART (for newly initiated patients) or at month 12 and 24 after the last viral load measurement (patients already on ART). If a viral load >1000 copies/ml is detected, the patient was called back for counselling for therapy adherence and repeat viral load measurement, 2 months after the initial viral load measurement. If the repeat viral load measurement was >1000 copies/ml after adherence counselling, this was taken to be indicative of therapy failure due to development of drug resistance and a switch to second-line therapy was made, together with intensified adherence counselling, without verifying the cause of virological failure by performing drug level testing or drug resistance testing. If viral load dropped to <1000 copies/ml after adherence counselling, the first-line treatment was maintained.

Parent study intervention arm

Patients randomly assigned to this arm were monitored using the investigational intensified monitoring strategy. This strategy consisted of 3-monthly viral load monitoring at month 9, 12, 15, 18, 21 and 24 (after start of ART in initiating patients or after the last viral load measurement in patients on ART). If a viral load measurement > 1000 copies/mL was detected, the patient was called back for a follow-up study visit at the next monthly medication collection visit (4 weeks after detection of elevated viral load). Upon arrival drug level testing was performed, repeated the viral load measurement, and a dried blood spot prepared and stored at room temperature. Procedures following this depended on the result of drug level testing:

If drug levels were detected by drug level testing, the result of the viral load measurement was awaited. If the repeat viral load was >1000 copies/ml, the dried blood spot was shipped directly by courier to the World Health Organization (WHO) reference laboratory for drug resistance testing. The reference laboratory provided feedback by means of a digital resistance report to the coordinating research physician. The patient would be called back for a second follow-up study visit

at the next monthly medication visit (8 weeks after detection of elevated viral load), either for prescription of second-line therapy or continuation of first-line therapy, guided by the result of resistance testing.

If drug level monitoring at the first follow-up visit indicated that drug levels were not detected, intensified counselling was performed at the same visit and first-line therapy was maintained, regardless of the result of the repeat viral load measurement. The patient would not be called back and the next viral load would be performed at the next scheduled three-monthly time point. However, if the viral load result at this visit was again >1000 copies/ml, drug resistance testing would be performed regardless of the outcome of drug level testing.

The study was conducted at the Ndlovu medical centre in the rural area of Elandsdoorn where adherence among people living with HIV has not been broadly investigated, which serves the larger Moutse area, situated in the Sekhukhune District Municipality in Limpopo province. It is estimated that the area has about 140-150,000 inhabitants of whom only 4% have tertiary education [27,28]. According to official statistics, almost half of adults are unemployed, and more than two-thirds of families live below the upper-bound poverty line (UBPL) income of 1183 ZAR ($70.90 per month) [1,28,29]. At the time of study, the HIV prevalence in the district was 8.1% of the total population [28], and approximately 3,600 PLHIV were receiving HIV treatment and care at Ndlovu Medical Centre. The ITREMA study enrolled adult PLHIV and assessed an intensified treatment monitoring strategy in a randomized comparison with a control group receiving standard-of-care HIV treatment in accordance with the South Africa National Department of Health guidelines [30]. Trial participants were followed up for 96 weeks.

Sample, Inclusion and Exclusion criteria

All records of participants who consented to enrolment in the ITREMA trial were included in our sub-study. The trial included adult participants (18 years and older) who were HIV positive and were either ART-naïve and ready to start treatment or had been on treatment for more than one year. As the trial intervention was deemed not to interfere with the predictor-outcome relationships assessed in the current study, participants were included regardless of randomization status.

Data Collection and Measures

Data were collected by a trained research assistant, and included sociodemographic and psychosocial characteristics, self-reported adherence difficulties, pill count and viral load information.

Sociodemographic characteristics

Collected information included age, gender, education level, employment status, income, income compositions and household income, number of household members and household composition,

and partnership status. Measures were adapted from the South African National Income Dynamics Study and the National Health Nutrition Survey [31,32]. Income data was entered in South African Rand (ZAR) and was converted to United States Dollar (USD) amounts using the approximate exchange rate at the time of start of study (12.30 ZAR to USD exchange rate, June 2015). Questions regarding food insecurity related to the availability of food in the participant's household. These included 1) Did your household run out of money to buy food during the past 12 months? (yes/no/do not know), 2) Has it happened in the past 30 days? (yes/no/do not know), 3) Has it happened 5 or more days in the past 30 days? (yes/no/do not know), 4) In the past 12 months, were there times when members of your household went hungry because there was not enough food in the house to eat? (yes/no/do not know), 5) Which were the months (in the last 12 months) in which you experienced a lack of food or money such that one or more members of your household had to go hungry? (January→December, do not know). Individuals were labeled to be food insecure if they answer "Yes" to all affirmative household food access scale of occurrence questions.

Psychosocial variables

Questionnaire item scores were each evaluated for consistency and distribution (Supplementary material 1). Some composite scores were dichotomized based on skewness of the distribution of the response. Sensitivity analyses of the univariate analyses and multivariable models for each outcome were performed in which all item scores were entered as continuous variables.

Adherence efficacy describes the attitude towards and expectations of the effect of ART that participants had prior to starting treatment. Adherence efficacy was measured with three items from the AIDS Clinical Trials Group (ACTG) questionnaire [33]: *"If you do not take this medication exactly as instructed, the HIV in your body will become resistant to HIV medication", "The medication will have a positive effect on your health",* and "*You will be able to take all or most of the medication as directed?".* Responses were measured on a four-point scale, from "not at all" (1) to "extremely sure" (4). Item scores were summed; a higher score indicated higher adherence efficacy (maximum score 12). The 3-item scale had good internal consistency (Cronbach's alpha = 0.87). Scores were dichotomised and values above 8 were classified as high adherence efficacy.

Support from household and non-household members were each assessed with five items from the Netherlands Kinship Panel Study, and included questions on support in making decisions about work/education, social, leisure time activities, and other personal matters [34], for instance: *"To what extent do persons in your household support you?" or "To what extent do family members who do not live in your household support you"?* Responses were given on a four-point scale, from 'no support (1)' to 'a lot of support (4)'. The two subscales each had good internal consistency (household members: Cronbach's alpha = 0.92; non-household members: Cronbach's alpha = 0.96). Item scores were averaged, and a higher score indicated more support from household or non-household

members (maximum score 20). Scores were dichotomised and values above 14 were classified as high household support.

Health literacy was assessed using the Brief Estimate of Health Knowledge and Action (BEHKA) HIV version [35]. This instrument was designed to assess HIV-related health knowledge and the ability to act in accordance with this knowledge, encompassing two subscales: theoretical knowledge (2 items) and operational knowledge (5 items). The following theoretical knowledge items are included: *"Is the goal of ARV's to make the CD4-count go UP or DOWN?", and "Is the goal of ARV's to make the viral load go UP or DOWN?"*. The theoretical knowledge items were scored as correct or incorrect and correct responses were summed. Operational knowledge questions included: *"I don't take my ARV's when they make me feel bad", "I don't take my ARV's when I am too tired", "I don't take my ARV's when I am feeling down or low", "I don't take my ARV's because it tastes bad", and "I don't take my ARV's when I feel good".* Responses to the operational knowledge items were given on a three-point scale ranging from "agree" (1) to "disagree" (3). The operational knowledge sub-scale had adequate internal consistency (Cronbach's alpha = 0.72). Three points were allocated per question where the answer was "disagree", 1 where the answer was "agree" and 2 points where the answer was "unsure". Final scores on the operational knowledge items were summed as follows: 0-3=low, 4-5=marginal and 6-8=adequate and a higher score indicated higher health literacy. The calculated composite score as per questionnaire instructions [35,36] (maximum score 8) was dichotomised and values above 6 were classified as high health literacy.

Clinician trust was assessed with the Revised Helping Alliance Questionnaires [37]. This 11-item instrument is designed to assess the relationship between a patient and their clinician and whether the patient trusts the clinician in terms of shared decision-making, discussing personal matters regarding HIV and ART, communication, and respect. In the context of our study, clinician referred to a clinician providing care to a participant at Ndlovu Medical Centre. The following are examples of items: '*a good relationship has formed with my clinician*' or '*I feel the clinician understands me.*' Responses were given on a six-point scale ranging from 'strongly disagree (1)' to 'strongly agree (6)'; The scale had a good internal consistency (Cronbach's alpha = 0.82). Item scores were summed (maximum score 66), and a higher score represented more trust in the clinician. Summary scores were dichotomised and values above 48 were classified as high clinician trust.

The Coping Inventory for Stressful Situations (CISS-21) was included to measure use of task-, emotion-, and avoidance-oriented coping strategies during a stressful situation, which were each measured with seven items (25, 26). Task-oriented coping refers to direct action to solve a particular problem (e.g., "I focus on the problem and see how I can solve it"), emotion-oriented coping refers to efforts to modify emotional states caused by stress (e.g., "I blame myself for being too emotional in the situation"), and avoidance-oriented coping refers to efforts to minimize distress by avoiding

the problem or finding distracting activities (e.g., "I take some time off and get away from the problem")[40]. Responses to items were given on a 5-point scale ranging from "never" (1) to "always (5)". The full scale had good overall internal consistency (Cronbach's alpha = 0.81), and the internal consistency of the subscales was adequate to good (task-oriented coping: Cronbach's alpha = 0.88; emotion-oriented coping: Cronbach's alpha = 0.74; avoidance-oriented coping: Cronbach's alpha = 0.74). Item scores were summed, and a higher score indicated a more frequent use of the specific coping strategy (maximum score per scale 56). Each subscale was entered as a separate continuous covariable to the statistical analysis.

HIV-related stigma was assessed using the 13-item scale developed by Kalichman et al [41], which focuses on internalized stigma and stigmatizing beliefs. Items include: *"people who have AIDS are dirty", "most people become HIV positive by being weak or foolish", "would you mind if people knew if your family member has HIV/AIDS"?* Responses were given on a 4-point scale ranging from "strongly disagree" (1) to "strongly agree" (4), with higher scores indicating more experienced stigma. The scale had good internal consistency (Cronbach's alpha = 0.87). A mean composite score was calculated and dichotomized along the median.

The 9-item Patient Health Questionnaire (PHQ) was used to assesses experienced depression [42]. Participants answered the following question for several depression-related symptoms: *"Over the last 2 weeks, how often have you been bothered by any of the following problems?"* Examples of symptoms include: *"Little interest or pleasure in doing things", "Feeling down, depressed, or hopeless", "Trouble falling or staying asleep, or sleeping too much", "Thoughts that you would be better off dead or of hurting yourself in some way".* Responses were given on a 4-point scale ranging from "not at all" (1), "several days" (2), "more than half the days" (3) to "nearly every day" (4). The results of one participant who refused to answer this questionnaire in full were excluded from this part of the analysis. The scale had adequate internal consistency (Cronbach's alpha = 0.78). Item scores were summed and dichotomized according to questionnaire instructions [36,42,43], with low scores (1-9) indicating minor to mild symptoms of depression and scores >9 indicating moderate or severe depressive symptoms (maximum score 27).

ART adherence and virological failure

Self-reported adherence difficulty was measured at three-monthly intervals between week 12 and 96 of follow-up using three items from the ACTG questionnaire [33] adopted in the CASE self-reported adherence index [44]: "*How often do you have difficulty in taking your medication on time"?*, with responses given on 4-point scale (1=all the time, 4= never, "*On average how many days per week would you say that you missed at least one dose of your medication?",* with responses given on a 6-point scale (1=every day, 6=never), and *"When was the last time you missed taking any of your medications?"*, with responses also given on a 6-point scale (1=past week, 6= never). Responding

'never' to all three questions at all timepoints was taken to indicate no self-reported adherence difficulties. Sensitivity analyses were conducted using the single item "*On average how many days per week would you say that you missed at least one dose of your medication?"* to assess whether adoption of a more immediate measure of short-term non-adherence would yield different results.

Suboptimal adherence as measured using pill count was measured at three-monthly intervals between week 12 and 96 of follow-up. Patients were instructed to return with leftover ART tablets. Tablets were counted and the number of doses taken during the last month was calculated as a percentage of the number of doses prescribed by a lay adherence, with 100% indicating complete adherence. Non-adherence was defined as a pill count <95% in accordance with the threshold used by the World Health Organization (WHO) [45].

The HIV-RNA load was measured at 6 months (24 weeks), 1 year, and 2 years after initiation of ART in newly initiated participants, and annually in participants already on ART. Virological failure was defined as viremia ≥1000 copies/ml, as defined by the WHO [46,47].

For each outcome, if the outcome definition occurred on at least one timepoint, the patient was marked as having met the outcome definition. Treatment arm allocation in the parent trial was not included as a covariate in the current analysis, as this variable was shown not to be significantly associated with virological failure, self-reported adherence difficulties or suboptimal adherence as measured using pill count [48].

Data analysis

Data were analyzed using STATA version 15.1. Frequencies were calculated to describe categorical variables while median and interquartile range were calculated for continuous variables. For univariable analysis of associations between outcomes (self-reported adherence difficulties, suboptimal adherence indicated by pill count and virological failure) and covariables, the Pearson Chi-square or Fischer's Exact test were used in case of dichotomous and categorical variables, and the Student's t-test in case of continuous covariables. Variables that were associated with the outcome with a significance level of <0.1 were subsequently included in a multivariable logistic regression analysis to assess independent associations; p <0.05 was considered statistically significant. Stratified analyses of female and male participants were performed. Adjusted odds ratios (aOR) and their corresponding 95% confidence intervals (95%CI) were reported.

Ethical Approval

Ethics approval for the ITREMA trial was obtained from the University of Pretoria Human Research Ethics Committee (Ref Number: 69/2015) and the Department of Health, Limpopo province (Ref No 4/2/2). Ethical clearance for this sub-study was obtained from the University of the Witwatersrand

Human Research Ethics Committee (M190641), and approval was provided by the Johannesburg Health District (DRC Ref: 2019-10-005, National Health Research Database Reference Number: GP_201910_031).

RESULTS

Patient characteristics

Participants' socio-demographic characteristics are presented in Table 1. Of the 501 participants included, 29.9% were male (150/501). Participants median age was 42 years (IQR 36-49 years); over half the participants were aged 35-49 years (51.3%, 257/501). Over half of participants (58.7%, 294/501) were in a relationship, which included being married, cohabiting, or having a partner but not living together. The majority (81.4%, 408/501) had a secondary (grade 8-12) or tertiary level of education, and 18.6% (93/501) had a primary education level (grade 0-7). More than half of participants (51.1%, 256/501) were unemployed. Over two-thirds of the participant households (69.1%, 346/501) earned less than the current South African minimum wage of 3500.00 ZAR (285 USD) per month, while 6.2% (31/501) households earned above 10,000 ZAR (813 USD) per month. In terms of social grants, about half of the study participants did not receive any grant (51.3%, 257/501), while 22.6% (113/501) received a child support grant, 18.0% (90/501) received an old age grant, and 3.2% (16/501) received a disability grant. The median number of people in participants' households was 5 (IQR=3-7). Less than 10% of the study participants reported food insecurity in the last 30 days (8.2%, 41/501). The majority of the study participants had adequate self-efficacy (94.2%, 472/502), high health literacy (98.8%, 487/501), high clinician trust (99.6%, 497/501), good household (86.8%, 434/501) and non-household support (60.9%, 305/501) (Table 1).

Assessments during follow-up of self-reported adherence difficulties and adherence indicated by pill count were available for 458 participants. Viral load data during follow-up were available for 436 participants. Overall, 53.1% (243/458) of participants self-reported adherence difficulties, 35.4% (162/458) had a pill count <95%, and 15.5% (n=68/436) experienced virological failure (≥1000 copies/ml).

Overlap between study outcomes

Of all study participants, 7.2% (36/501) met all three study outcomes, 28.3% (142/501) had both self-reported non-adherence and suboptimal pill count, 10.0% (50/501) had both self-reported non-adherence and virological failure, and 7.2% (36/501) reported suboptimal pill count and virological failure.

Test of association analysis

Findings of analyses of covariates of self-reported adherence difficulties, pill count and virological failure are shown in Table 1. Self-reported adherence difficulties were more likely in male compared

to female participants (coefficient=0.56, p=0.008, chi=7.052). Suboptimal adherence as indicated by a pill count <95% was also more likely in male participants (coefficient=0.48, p=0.023, chi=5.187). Suboptimal pill count adherence was inversely associated with household income (coefficient= -0.063, p=0.021, chi=2.378) and use of task-oriented coping (coefficient= -0.032, p=0.025, chi=2.246) and these factors where thus protective against suboptimal pill count adherence. Virological failure was again more likely in male participants (coefficient=0.68, p=0.014, chi=6.338). In addition, there was a strong association between the presence of moderate or severe depressive symptoms and virological failure. These were present in 13.2% [9/68] of participants with virological failure versus 4.6% [17/368] of participants without virological failure (coefficient=1.14, p=0.009, chi=7.556). Univariate findings between the predictor variables and the outcomes demonstrated similar associations (Supplementary material 2).

Table 1: Sample characteristics and univariable analyses of sociodemographic and psychosocial factors associated with self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

	Overall sample, n (%) or median [IQR]	Self-reported adherence difficulties (n=458)						Pill count (n=458)						VIRAL LOAD (n=436)					
		Poor self-reported adherence (n=243, 53.1%)	%	Good self-reported adherence (n=215, 46.9%)	%	p-value	Chi-square value/ t value	Pill count <95% (n=162, 35.4%)	%	Pill count ≥95% (n=296, 64.6%)	%	p-value	Chi-square value/ t value	VL ≥1000 (n=68, 15.6%)	%	VL <1000 (n=368, 84.4%)	%	p value	Chi-square value/ t value
Sociodemographic characteristics																			
Gender (male)	150 (29.9%)	84	34.6	50	23.3	0.008	7.052	58	35.8	76	25.7	0.023	5.187	29	42.7	101	27.5	0.014	6.338
Age (median)	42.0 years [36.0-49.0 years]	42 (37-49)	-	43 (36-50)	-	0.521	0.640	42 (36-48)	-	43 (36-50)		0.250	1.153	41 (36-49)	-	43 (37-50)	-	0.188	1.319
Age (category)																			
<35 years	114 (22.8)	51	21.0	44	20.63			33	20.4	62	21.0			13	19.1	74	20.1		
35-49 years	257 (51.3)	134	55.1	107	50.67			95	58.6	146	49.3			38	55.9	193	52.5		
>50 years	130 (26.0)	58	23.9	64	28.70			34	21.0	88	29.7			17	25.0	101	27.5		
Relationship status (in a relationship)	294 (58.7)	145	59.7	126	58.6	0.817	0.054	97	59.9	174	58.8	0.820	0.052	37	54.4	221	60.1	0.421	0.756
Education (secondary/tertiary)	408 (81.4)	197	81.1	176	81.9	0.828	0.047	134	82.7	239	80.7	0.604	0.270	59	86.7	295	80.2	0.201	1.638
Employment (unemployed)	256 (51.1)	124	51.0	108	50.2	0.865	0.029	87	53.7	145	49.0	0.334	0.932	40	58.8	182	49.5	0.187	2.015
Household income median (ZAR) (median)	R1600.00 [R700.00-R4200.00]	1500 (660-4000)		1600 (720-4300)		0.851	0.188	1500 (660-3500)		1800 (710-4500)		0.021	2.378	1500 (510-4500)		1500 (700-4000)		0.629	0.482
Household income per month (category)																			
<3,500 ZAR	346 (69.1)	172	70.8	147	68.4			121	74.7	198	66.9			46	67.7	260	70.7		
3,500-10,000 ZAR	124 (24.8)	55	22.6	58	27.0			36	22.2	77	26.0			18	26.5	88	23.9		
>10,000 ZAR	31 (6.2)	16	6.6	10	4.7			5	3.1	21	7.1			4	5.9	20	5.4		
Social grants																			
No grants	257 (51.3)	124	51.0	113	52.6	0.925	0.928	90	55.7	147	49.7	0.579	3.118	32	47.1	192	52.2	0.338	3.980
Child related grant	113 (22.6)	57	23.5	45	20.9			32	19.8	70	23.7			18	26.5	81	22.0		

Old-age related grant	90 (18.0)	42	17.3	42	19.5			31	19.1	53	17.9			10	14.7	72	19.6		
Other grants	25 (5.0)	12	4.9	9	4.2			6	3.7	15	5.1			5	7.4	14	3.8		
Disability grant	16 (3.2)	8	3.3	6	2.8			3	1.9	11	3.7			3	4.4	9	2.5		
Number of people living together (median)	5 people [3-7 people]	5 (3-7)		5 (3-7)		0.157	1.416	5 (3-7)		5 (3-7)		0.053	1.940	5 (4-7)		5 (3-7)		0.295	-1.049
Number of people living together (category)																			
1-2	58 (11.6)	29	11.9	22	10.2			23	14.2	28	9.5			6	8.8	42	11.4		
3-5	233 (46.5)	115	47.3	98	45.6			74	45.7	139	47.0			31	45.6	172	46.7		
Above 5	210 (41.9)	99	40.7	95	44.2			65	40.1	129	43.6			31	45.6	154	41.9		
Food insecurity (in the last 30 days)	41 (8.2)	18	7.4	18	8.4	0.731	0.147	16	9.9	20	6.8	0.276	1.407	9	13.2	26	7.1	0.092	2.960
Psychosocial characteristics																			
Adherence self-efficacy (adequate)	472 (94.2)	226	93.0	208	96.7	0.093	3.213	150	92.6	284	96.0	0.130	2.371	66	97.1	350	95.1	0.752	0.499
Health literacy (high)	487 (98.8)	236	98.3	210	99.1	0.508	0.450	155	97.5	291	99.3	0.129	2.644	66	98.5	358	98.6	0.941	0.0054
Clinician trust (high)	497 (99.6)	242	100.0	213	99.5	0.469	1.133	161	100.0	294	99.7	1.000	0.547	68	100.0	365	99.7	1.000	0.186
Household support (good)	434 (86.8)	226	93.0	197	92.1	0.724	0.279	154	95.1	269	90.9	0.091	1.440	58	85.3	317	86.4	0.630	0.057
Non-household family support (good)	305 (60.9)	176	72.7	157	73.0	1.000	0.0093	119	73.5	214	72.5	0.912	0.285	41	60.3	227	61.7	0.555	0.047
Coping strategy scores																			
Task-oriented coping (median)	26 (21-33)	26 (20-32)		27 (21-33)		0.058	1.901	25 (20-32)		27 (22-33)		0.025	2.246	25 (20-31)		27 (21-33)		0.051	1.956
Emotion oriented coping (median)	18 (14-22)	17 (14-21)		18 (15-22)		0.099	1.654	17 (14-21)		18 (14-22)		0.514	0.653	17.5 (14-20)		18 (14-22)		0.059	1.891
Avoidance oriented coping (median)	15 (12-20)	15.5 (12-20)		15 (12-20)		0.979	-0.0262	15 (11-20)		15 (12-20)		0.852	0.187	14 (11-19.5)		15 (12-20)		0.256	1.138
HIV-related (internalized) stigma (stigma)	258 (51.8)	132	54.6	100	46.7	0.096	2.776	92	56.8	140	47.6	0.061	3.515	41	60.3	180	49.2	0.094	2.834
Mental Health (moderate or severe depressive symptoms)	31 (6.2)	18	7.4	9	4.2	0.146	2.166	14	8.7	13	4.4	0.067	3.475	9	13.2	17	4.6	0.009	7.556

Table 1a: Male: Sample characteristics and univariable analyses of sociodemographic and psychosocial factors associated with self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

		Self-reported adherence difficulties (n=458)						Pill count (n=458)						VIRAL LOAD (n=436)					
	Overall sample, n (%) or median [IQR]	Poor self-reported adherence (n=243, 53.1%)	%	Good self-reported adherence (n=215, 46.9%)	%	p-value	Chi-square value/ t value	Pill count <95% (n=162, 35.4%)	%	Pill count ≥95% (n=296, 64.6%)	%	p-value	Chi-square value/ t value	VL ≥1000 (n=68, 15.6%)	%	VL <1000 (n=368, 84.4%)	%	p value	Chi-square value/ t value
Sociodemographic characteristics																			
Gender (male)	150 (29.9%)	84	34.6	50	23.3	0.008	7.052	58	35.8	76	25.7	0.023	5.187	29	42.7	101	27.5	0.014	6.338
Age (median)	43.0 years [37.0-50.0 years]	42 (37.5-50)	-	44 (38-53)	-	0.263	1.124	42 (38-49)	-	44 (37-51.5)		0.364	0.910	40 (36-48)	-	44 (38-51)	-	0.065	1.861
Age (category)																			
<35 years	28 (18.7)	14	16.7	9	18.0			9	15.5	14	18.4			6	20.7	17	16.8		
35-49 years	77 (51.3)	47	56.0	23	46.0			34	58.6	36	47.4			16	55.2	50	49.5		
>50 years	45 (30.0)	23	27.3	18	36.0			15	25.9	26	34.2			7	24.1	34	33.7		
Relationship status (in a relationship)	88 (58.7)	53	63.1	29	58.0	0.558	0.342	37	63.8	45	59.2	0.721	0.291	18	61.4	62	62.1	1.000	0.004
Education (secondary/tertiary)	108 (80.6)	69	82.1	39	78.0	0.653	0.344	46	79.3	62	81.6	0.827	0.108	25	86.2	79	78.2	0.436	0.899
Employment (unemployed)	79 (52.7)	42	50.0	25	50.0	1.000	0.000	35	60.3	32	42.1	0.055	4.377	19	65.52	45	44.55	0.047	3.961
Household income median (ZAR) (median)	R1500.00 [R500.00-R3900.00]	1500 (450-3500)		1500 (360-3900)		0.616	-0.502	1400 (330-2000)		1850 (650-4585)		0.005	2.860	1500 (0-3500)		1500 (600-3800)		0.692	0.397
Household income per month (category)																			
<3,500 ZAR	104 (69.3)	62	73.8	32	64.0			46	60.5	48	82.8			20	69.0	72	71.3		
3,500-10,000 ZAR	41 (27.3)	17	20.2	18	36.0			26	34.2	9	15.5			7	24.1	26	25.7		
>10,000 ZAR	5 (3.3)	5	6.0	0	0.0			4	5.3	1	1.7			2	6.9	3	2.3		
Social grants																			
No grants	69 (46.0)	37	44.1	26	52.0			28	48.3	35	46.1			15	51.7	46	45.5		
Child related grant	35 (23.3)	19	22.6	13	26.0			10	17.2	22	29.0			8	27.6	24	23.8		
Old-age related grant	30 (20.0)	17	20.2	8	16.0	0.719	2.390	12	20.7	13	17.1	0.386	4.175	3	10.3	21	20.8	0.770	
Other grants	11 (7.3)	7	8.3	2	4.0			6	10.3	3	4.0			2	6.9	6	5.9		

Disability grant	5 (3.3)	4	4.8	1	2.0			2	3.5	3	4.0			1	3.5	4	4.0		
Number of people living together (median)	5 people [3-7 people]	5 (3-6.5)		5 (3-7)		0.385	0.872	4 (3-6)		5 (3-7)		0.245	1.167	5 (4-7)		5 (3-7)		0.746	-0.324
Number of people living together (category)																			
1-2	21 (14.0)	11	13.1	7	14.0			8	13.8	10	13.1			2	6.9	15	14.9		
3-5	71 (47.3)	42	50.0	23	46.0			29	50.0	36	47.4			17	58.6	47	46.5		
Above 5	58 (38.7)	31	36.9	20	40.0			21	36.2	30	39.5			10	34.5	39	38.6		
Food insecurity (in the last 30 days)	15 (10.0)	9	10.7	2	4.0	0.209	1.875	9	15.5	2	2.6	0.010	7.248	6	20.7	5	5.0	0.015	7.205
Psychosocial characteristics																			
Adherence self-efficacy (adequate)	139 (92.3)	76	90.5	49	98.0	0.153	2.832	54	93.1	71	93.4	1.000	0.005	28	96.6	94	93.1	0.683	0.473
Health literacy (high)	145 (98.0)	80	96.4	50	100.0	0.291	1.849	55	96.5	75	98.7	0.576	0.711	27	96.4	99	98.0	0.523	0.244
Clinician trust (high)	150 (100.0)	84	100.0	50	100.0	-		58	100.0	76	100.0	-		29	100.0	101	100.0	-	
Household support (good)	122 (81.9)	68	81.0	40	81.6	1.000	0.009	46	80.70	62	81.58	1.000	0.016	23	79.3	81	81.0	0.796	0.041
Non-household family support (good)	92 (61.3)	51	60.7	29	58.0	0.856	0.096	32	55.17	48	63.16	0.378	0.872	17	58.6	61	60.4	1.000	0.030
Coping strategy scores																			
Task-oriented coping (median)	27 (21-34)	26 (20-32)		30.5 (23-34)		0.034	2.144	26.5 (20-34)		27 (22-34)		0.518	0.647	26 (19-31)		27 (21-34)		0.131	1.521
Emotion oriented coping (median)	18 (14-21)	18 (14-21)		18 (14-21)		0.931	0.086	18 (14-21)		18 (14-22)		0.743	0.329	18 (14-20)		17 (14-22)		0.549	0.601
Avoidance oriented coping (median)	15 (12-20)	16 (12-20)		13 (12-17)		0.095	-1.684	14.5 (11-20)		15 (12-19)		0.560	0.584	14 (10-17)		15 (13-19)		0.159	1.417
HIV-related (internalized) stigma (stigma)	86 (57.7)	50	60.2	24	48.0	0.208	1.894	34	58.6	40	53.3	0.599	0.371	18	62.1	53	53.0	0.406	0.747
Mental Health (moderate or severe depressive symptoms)	11 (7.3)	6	7.1	4	8.0	1.000	0.033	6	10.3	4	5.3	0.328	1.230	4	13.8	5	5.0	0.111	2.734

Table 1b: female: Sample characteristics and univariable analyses of sociodemographic and psychosocial factors associated with self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

	Overall sample, n (%) or median [IQR]	Self-reported adherence difficulties (n=458)						Pill count (n=458)						VIRAL LOAD (n=436)					
		Poor self-reported adherence (n=243, 53.1%)	%	Good self-reported adherence (n=215, 46.9%)	%	p-value	Chi-square value/ t value	Pill count <95% (n=162, 35.4%)	%	Pill count ≥95% (n=296, 64.6%)	%	p-value	Chi-square value/ t value	VL ≥1000 (n=68, 15.6%)	%	VL <1000 (n=368, 84.4%)	%	p value	Chi-square value/ t value
Sociodemographic characteristics																			
Gender (female)	351 (70.1%)	159	65.4	165	76.7	0.008	7.052	104	64.2	220	74.3	0.023	5.187	39	57.4	267	72.6	0.014	6.338
Age (median)	42.0 years [35.0-49.0 years]	42 (36-49)	-	43 (35-50)	-	0.829	0.216	42.5 (35-48)	-	42.5 (36-50)		0.362	0.913	42 (36-49)	-	43 (36-49)	-	0.746	0.324
Age (category)																			
<35 years	86 (24.5)	37	23.3	35	21.2			24	23.1	48	21.8			7	18.0	57	21.4		
35-49 years	180 (51.3)	87	54.7	84	50.9			61	58.7	110	50.0			22	56.4	143	53.5		
>50 years	85 (24.2)	35	22.0	46	27.9			19	18.2	62	28.2			10	25.6	67	25.1		
Relationship status (in a relationship)	206 (58.7)	92	57.9	97	58.8	0.910	0.029	60	57.7	129	58.6	0.904	0.026	19	48.7	159	59.6	0.226	1.641
Education (secondary/tertiary)	265 (81.8)	128	80.5	137	83.0	0.568	0.347	88	84.6	177	80.5	0.441	0.821	34	87.2	216	80.9	0.505	0.898
Employment (unemployed)	177 (50.4)	82	51.6	83	50.3	0.825	0.052	52	50.0	113	51.4	0.905	0.053	21	53.9	137	51.3	0.767	0.088
Household income median (ZAR) (median)	R1800.00 [R1000.00-R4345.00]	1600 (720-4000)		1900 (1050-4345)		0.759	0.308	1650 (1000-4000)		1800 (1000-4422)		0.375	0.889	1700 (1000-5200)		1600 (720-4200)		0.899	0.127
Household income per month (category)																			
<3,500 ZAR	242 (69.0)	110	69.1	115	69.7			73	70.1	152	69.1			26	66.7	188	70.4		
3,500-10,000 ZAR	83 (23.7)	38	23.9	40	24.2			27	26.0	51	23.2			11	28.2	62	23.2		
>10,000 ZAR	26 (7.4)	11	7.0	10	6.1			4	3.9	17	7.7			2	5.1	17	6.4		

Social grants																		
No grants	188 (53.6)	87	54.7	87	52.7			62	59.6	112	50.9			17	43.6	146	54.7		
Child related grant	78 (22.2)	38	23.9	32	19.4			22	21.2.	48	21.8			10	25.6	57	21.4		
Old-age related grant	60 (17.1)	25	15.7	34	20.6	0.695	2.221	19	18.3	40	18.2	0.053	8.503	7	18.0	51	19.1	0.214	4.760
Other grants	14 (4.0)	5	3.1	7	4.2			0	0	12	5.5			3	7.7	8	3.0		
Disability grant	11 (3.1)	4	2.5	5	3.0			1	1.0	8	3.6			2	5.1	5	1.9		
Number of people living together (median)	5 people [3-7 people]	5 (3-7)		5 (3-7)		0.345	0.945	5 (3-7)		5 (3-7)		0.160	1.407	6 (4-7)		5 (3-7)		0.203	-1.276
Number of people living together (category)																			
1-2	37 (10.5)	18	11.3	15	9.0			15	14.4	18	8.18			4	10.3	27	10.1		
3-5	162 (46.2)	73	45.9	75	45.5			45	43.3	103	46.8			14	35.9	125	46.8		
Above 5	152 (43.3)	68	42.8	75	45.5			44	42.3	99	45.0			21	53.9	115	43.1		
Food insecurity (in the last 30 days)	26 (7.4)	9	5.7	16	9.7	0.213	1.852	7	6.7	18	8.2	0.824	0.209	3	7.7	21	7.9	1.000	0.0014
Psychosocial characteristics																			
Adherence self-efficacy (adequate)	333 (94.9)	150	94.3	159	96.4	0.437	0.751	96	92.3	213	96.8	0.090	3.254	38	97.4	256	95.9	1.000	0.219
Health literacy (high)	342 (99.1)	156	99.4	160	98.8	1.000	0.306	100	98.0	216	99.5	0.241	1.676	39	100.0	259	98.9	1.000	0.451
Clinician trust (high)	347 (99.4)	158	100.0	163	99.4	1.000	0.966	103	100.0	218	99.5	1.000	0.472	39	100.0	264	99.6	1.000	0.148
Household support (good)	312 (88.9)	68	81.0	40	81.6	1.000	1.293	98	94.2	191	86.8	0.055	4.027	35	89.7	236	88.4	1.000	0.062
Non-household family support (good)	213 (60.7)	97	61.0	101	61.2	1.000	0.001	69	66.4	129	58.6	0.222	1.766	24	61.5	166	62.2	1.000	0.006
Coping strategy scores																			

Task-oriented coping (median)	26 (21-32)	25.5 (20.5-32)		27 (21-33)		0.339	0.958	25 (20-31)		27 (22-33)		0.017	2.391	24 (20-31)		27 (21-33)		0.193	1.306
Emotion oriented coping (median)	18 (14-22)	17 (14-21)		19 (15-22)		0.078	1.767	17 (14-21)		18 (14-22)		0.657	0.444	17 (14-19)		18 (14-22)		0.068	1.831
Avoidance oriented coping (median)	15 (12-20)	15 (11-19)		16 (12-20)		0.367	0.903	15 (11-20)		15 (12-20)		0.833	-0.210	14 (11-21)		16 (12-20)		0.789	0.268
HIV-related (internalized) stigma	172 (49.3)	82	51.6	76	46.3	0.374	0.884	58	55.8	100	45.7	0.096	2.883	23	59.0	172	47.7	0.231	1.716
Mental Health (moderate or severe depressive symptoms)	20 (5.7)	12	7.6	5	3.0	0.082	3.373	8	7.8	9	4.1	0.186	1.901	5	12.8	12	4.5	0.051	4.462

Multivariable analysis

Results of multivariable logistic regression analyses of correlates of self-reported adherence difficulties, suboptimal adherence indicated by pill count and virological failure are shown in Table 2. For self-reported adherence difficulties, the only independent risk factor was male gender (aOR 1.78 [95%CI 1.17-2.71]; p=0.007, z=2.67). Male gender also was an independent risk factor for poor adherence as indicated by pill count <95% (aOR 1.57 [95%CI 1.02-2.41]; p=0.040, z=2.06), while higher household income (aOR 0.94 [95%CI 0.89-0.99]; p=0.030, z= -2.26) and higher task-oriented coping (aOR 0.97 [95%CI 0.94-1.00]; p=0.031, z= -2.16) were found to be protective factors against suboptimal adherence indicated by pill count <95%. Independent risk factors for virological failure were male gender (aOR 1.95 [95%CI 1.13-3.36]; p=0.017, z=2.39) and moderate or severe depressive symptoms (aOR 2.92 [95%CI 1.17-7.79]; p=0.021, z=2.30). Stratified analyses by sex showed that virological failure was more likely in males who reported food insecurity in the last 30 days (aOR 5.74 [95%CI 1.49-22.05]; p=0.011, z=2.54) and in females reporting depression (aOR 3.32 [95%CI 1.02-10.82]; p=0.046, z=1.99).

Table 2: Multivariable analyses of sociodemographic and psychosocial factors associated with of self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

Variable	Self-reported adherence difficulties			Pill count <95%			Virological failure (≥1000 copies/ml)		
	Adjusted Odds Ratio (95% CI)	p-value	z value	Adjusted Odds Ratio (95% CI)	p-value	z value	Adjusted Odds Ratio (95% CI)	p-value	z value
Gender									
Female	Ref	-	-	Ref	-		Ref	-	
Male	1.78 (1.17-2.71)	0.007	2.67	1.57 (1.02-2.41)	0.040	2.06	1.95 (1.13-3.36)	0.017	2.39
Household income (per 1000 ZAR)	-	-	-	0.94 (0.89-0.99)	0.024	-2.26	-	-	
Number of people living together	-	-	-	0.94 (0.87-1.01)	0.074	-1.78	-	-	-
Adherence self-efficacy									
Inadequate adherence self-efficacy	Ref		-	-	-	-	-	-	-
Adequate adherence self-efficacy	0.56 (0.22-1.44)	0.231	-1.20	-	-	-	-	-	-
Household family support									
Poor household family support	-	-	-	Ref	-	-	-	-	-
Household family support	-	-	-	1.54 (0.82-2.88)	0.179	1.40	-	-	-
Coping strategy scores (CISS)									
Task-oriented coping	0.80 (0.54-1.19)	0.248	-1.16	0.97 (0.94-1.00)	0.031	-2.16	0.98 (0.94-1.01)	0.230	-1.20
Emotion-oriented coping	0.77 (0.53-1.13)	0.234	-1.19	-	-	-	0.95 (0.90-1.01)	0.093	-1.68
Food insecurity in the last 30 days									
No reported food insecurity in the last 30 days	-	-	-	-	-	-	Ref	-	
Reported food insecurity in the last 30 days	-	-	-	-	-	-	1.76 (0.75-4.10)	0.193	1.30
HIV related stigma									
No reported stigma	Ref	-	-	Ref		-	Ref	-	-
Reported stigma	1.18 (0.80-1.75)	0.401	0.84	1.22 (0.81-1.85)	0.341	0.52	1.29 (0.64-2.61)	0.471	0.72
Mental Health									
Minimal or no depressive symptoms	-	-	-	Ref	-	-	Ref	-	-
Moderate or severe depressive symptoms	-	-	-	1.93 (0.85-4.37)	0.114	1.62	2.92 (1.17-7.29)	0.021	2.30

Table 2a: Male: Multivariable analyses of sociodemographic and psychosocial factors associated with of self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

Variable	Self-reported adherence difficulties			Pill count <95%			Virological failure (≥1000 copies/ml)		
	Adjusted Odds Ratio (95% CI)	p-value	z value	Adjusted Odds Ratio (95% CI)	p-value	z value	Adjusted Odds Ratio (95% CI)	p-value	z value
Age	-	-		-	-	-	0.97 (0.93-1.01)	0.123	-1.54
Employment (unemployed)	-	-		1.24 (0.56-2.74)	0.592	0.54	1.86 (0.76-4.58)	0.177	1.35
Household income (per 1000 ZAR)	-	-	-	0.84 (0.72-0.98)	0.028	-2.20	-	-	-
Coping strategy scores (CISS)									
Task-oriented coping	0.95 (0.90-1.00)	0.041	-2.04	-	-		-	-	-
Emotion-oriented coping	1.00 (0.93-1.08)	0.929	0.09	-	-		-	-	-
Food insecurity in the last 30 days									
No reported food insecurity in the last 30 days	-	-		-	-	-	Ref	-	-
Reported food insecurity in the last 30 days	-	-	-	6.34 (1.18-34.09)	0.031	2.15	3.98 (1.07-14.89)	0.040	2.05

Table 2b: Female: Multivariable analyses of sociodemographic and psychosocial factors associated with of self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

Variable	Self-reported adherence difficulties			Pill count <95%			Virological failure (≥1000 copies/ml)		
	Adjusted Odds Ratio (95% CI)	p-value	z value	Adjusted Odds Ratio (95% CI)	p-value	z value	Adjusted Odds Ratio (95% CI)	p-value	z value
Social grants									
Child related grant	-	-	-	Ref	-		-	-	-
Disability grant	-	-	-	0.21 (0 .02-1.96)	0.173	-1.36	-	-	-
No grants	-	-	-	1.37 (0 .73-2.56)	0.323	0.99	-	-	-
Old-age related grant	-	-	-	1.46 (0 .65-3.29)	0.356	0.92	-	-	-
Other grants	-	-	-	1	-	-	-	-	-
Adherence self-efficacy									
Inadequate adherence self-efficacy	-	-	-	Ref	-	-	-	-	-
Adequate adherence self-efficacy	-	-	-	0.36 (0.11-1.21)	0.100	-1.64	-	-	-
Household family support									
Poor household family support	-	-	-	Ref	-	-	-	-	-
Household family support	-	-	-	2.43 (0.95-6.20)	0.064	1.85	-	-	-
Coping strategy scores (CISS)									
Task-oriented coping	-	-	-	0.96 (0.92-1.00)	0.045	-2.01	-	-	
Emotion-oriented coping	0.96 (0.92-1.00)	0.056	-1.91	-	-	-	0.93 (0.87-1.00)	0.046	-1.99
HIV related stigma									
No reported stigma	-	-	-	Ref	-	-	-	-	-
Reported stigma	-	-	-	1.13 (0.66-1.92)	0.653	0.45	-	-	-
Mental Health									
Minimal or no depressive symptoms	Ref	-	-	-	-	-	Ref	-	-
Moderate or severe depressive symptoms	2.93 (0.99-8.64)	0.051	1.95	-	-	-	3.58 (1.15-11.10)	0.027	2.21

Sensitivity analyses

When all psychosocial characteristics were entered as continuous measures to univariate and multivariable analysis, results for the outcomes of self-reported adherence difficulties and virological failure remained essentially unchanged (Supplementary materials 2 & 3). For suboptimal adherence as indicated by pill count <95%, the associations in univariate and multivariable analysis with gender and household income remained consistent. However, the association with task-oriented coping remained present in univariate analysis but not in multivariable analysis. Instead, the multivariable analysis for this outcome revealed associations with health literacy and household family support (Supplementary materials 2 and 3).

Sensitivity analysis using a self-reported adherence variable that considers only short-term adherence demonstrated a prevalence of self-reported short-term non-adherence of 51.3% (235/458) versus a prevalence of 53.1% (243/458) for the definition of self-reported adherence difficulties that was used in the main analysis. Univariate associations and multivariable model results with this outcome were consistent with the results of the main analysis (Supplementary materials 4).

DISCUSSION

Our study has assessed rates and sociodemographic and psychosocial factors associated with non-adherence as measured through self-report and pill count and virological failure among PLHIV in a South African rural population. We identified several demographic, socio-economic, and behavioural risk factors for non-adherence and virological failure and showed that there is limited overlap of markers of adherence with virological failure. We found that male gender was an independent risk factor for all outcomes. Depressive symptoms were independently associated with virological failure while household income and task-oriented coping score were protective against suboptimal pill-count adherence.

In multivariable analyses we found that self-reported adherence difficulties, suboptimal pill count adherence and virological failure were more likely in men than women. The finding of increased problems with adherence to ART in men is consistent with other studies conducted in rural settings and may reflect poorer healthcare behaviour in men [15,49–56]. Several studies performed in different cultural contexts have identified underlying reasons for the generally poorer healthcare behaviour of men [4,57–59]. For men in rural settings in particular these include lack of time, poor healthcare access due to social constructions of masculinity, underlying cultural reasons, distance needed to travel to access care, and the lack of male care providers [4,15,57,58,60,61]. Men from rural settings report more severe barriers to care than their urban counterparts [13,62], highlighting the need to acknowledge how masculinity serve as a barrier for

rural men's access to ART services and prioritize rural men for interventions promoting ART adherence [58].

Suboptimal adherence as indicated by pill count was associated with low household income, as also found by other studies [44,63]. These findings confirm that despite the scale up of free ART in South Africa, financial constraints remain a barrier to ART adherence. Concerns around low household income in rural settings are centered on cost of seeking treatment, the distance needed to travel to access care, reliance on traditional medicine and the cost of food. [44]. At first sight, our finding that in stratified analysis the risk of virological failure was higher among male participants with food insecurity seems to be a result of this same dynamic. However, this finding is at odds with other studies reporting that women, not men, are less favored in terms of household food distribution and that mechanisms for how food insecurity impacted adherence were generally similar among women and men [64,65]. Nonetheless, our results suggest that there is a link between gender, food insecurity and ART adherence, heightening the importance of addressing food insecurity as part of comprehensive care among PLHIV. Further research should also examine how the negative impact of food unavailability on adherence in food-stressed households can be mitigated. Programmatic models that have been successful in rural settings, aiming to improve food security and nutrition in an HIV context include: 1) Nutrition supplementation interventions targeted to undernourished PLHIV, often using specialized foods, with nutrition assessment, counselling and support as a central component targeted to all PLHIV regardless of nutrition status. 2) Safety nets (food, cash transfer or vouchers), targeted to HIV-affected households and individuals (such as Orphans and Vulnerable Children) to improve household food security, mitigate the impact of HIV, and 3) Livelihood interventions targeted to PLHIV households or communities heavily affected by the AIDS epidemic [66].

In this cohort, better adherence as indicated by pill count was associated with increased use of task-oriented coping. This was more evident in female participants. This suggests that counselling strategies addressing specific coping styles could have a positive effect on ART treatment outcomes. Moreover, it is likely that there also are indirect associations between coping strategies, sex, and adherence to treatment through markers of mental health. More research is needed to assess these relationships and guide future interventions.

Furthermore, we found that the risk of virological failure was higher among participants with moderate or severe depressive symptoms. In stratified analysis, we found that while the prevalence of depressive symptoms was similar between men and women, the association was significant among female participants only. These findings are comparable to those of several studies assessing risk factors for non-adherence in PLHIV, which also found evidence that depression was associated with poor outcomes for HIV-infected patients on ART, especially in

women [67,68]. Our results suggest that, despite substantial progress made in quality and access to HIV related health care [69] as seen with recent transition to a DTG-based regimen [70], depression and other mental health problems remain underdiagnosed and often untreated among rural PLHIV [13,71]. There hence remains a critical need to screen for and treat depressive symptoms in PLHIV. The association between depression, sex and markers of suboptimal adherence indicate that screening for mental health problems should be considered as an integral part of adherence counselling, and that treatment of these problems could potentially improve adherence to ART.

We encountered high levels of both self-reported adherence difficulties as well as suboptimal adherence as measured through pill count in this setting. In contrast, rates of virological failure in this cohort were more limited. While self-reported adherence difficulties and suboptimal pill count results were significantly correlated with each other and with virological failure, overlap between these outcomes was limited. Sensitivity analysis showed similar findings for self-reported adherence difficulties. Various studies have reported significant correlations between objective and self-report measures of ART adherence [72–74], even though some studies conducted in developed and developing settings suggest that viral load is more likely to be accurate in terms of reflecting true adherence rates than self-reported adherence [8,75]. Previous research conducted in sub-Saharan African countries has also found that self-reported adherence tended to over or under-estimate adherence and is not necessarily associated with the virological suppression status of patients [76–79]. Factors that may affect the reliability of self-reported adherence and pill counts are numerous, and include variation in measurement methods and thresholds, social desirability bias, healthcare worker trust, and recall error.

Limitations and strengths

This study included participants receiving clinical care in a medical centre in rural Limpopo, South Africa. Therefore, findings from this study may not be generalizable to other rural settings in South Africa, or to other country settings. While the study assessed a broad range of psychosocial factors, the many individual, social and structural factors that may be of influence cannot feasibly be assessed in a single study. Therefore, the scope of covariates, while broad, by definition, and inevitably is limited. Potential covariates of ART adherence were assessed through self-report, which may have been affected by memory bias and social desirability bias. This study also highlights the practical limitations of conducting pill counts. In many cases patients forgot to take their left-over medication to their clinical visit. Previous studies used unannounced pill count to avoid this practical limitation, but this may not be feasible in practice.

CONCLUSION

This study in a rural community of people with HIV found that PLHIV who were male, had low household income or experienced moderate or severe depressive symptoms were at increased risk of suboptimal adherence and/or virological failure, and may benefit from additional ART adherence support. Sex-specific risk factors that were identified included depressive symptoms in women and food insecurity in men. Task-oriented coping was protective against suboptimal adherence as indicated by pill count. While the rate of self-reported adherence difficulties was high, there was limited overlap between risk factors for non-adherence and virological failure. The high levels of self-reported adherence difficulties would point to a possible self-reporting bias resulting in an over-estimation of bias adherence problems. Our identification of socio-demographic and psychosocial risk factors can guide the targeting of adherence support interventions to rural populations, as well as highlight the factors underlying adherence problems that should be addressed in such interventions. Our findings contribute to the available knowledge on risk factors for adverse outcomes of ART in rural populations and may contribute to the ongoing development of 'rural proof' healthcare policies currently being introduced in South Africa, such as National Health Insurance and the new 2030 Human Resources for Health Strategy.

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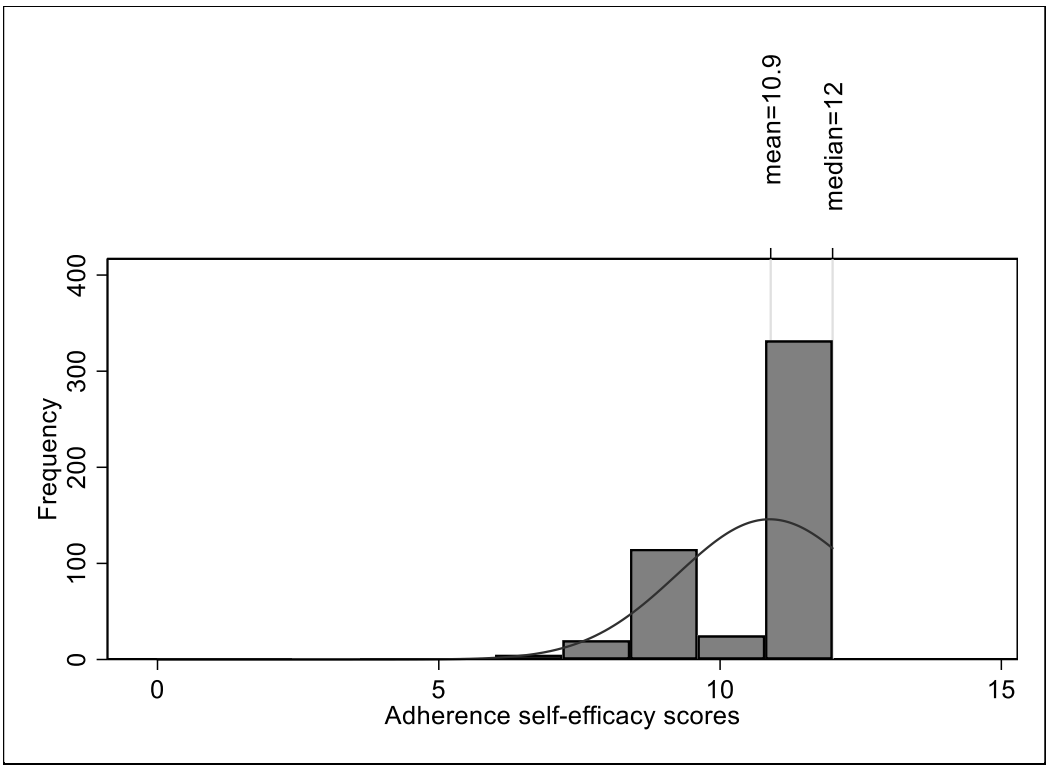
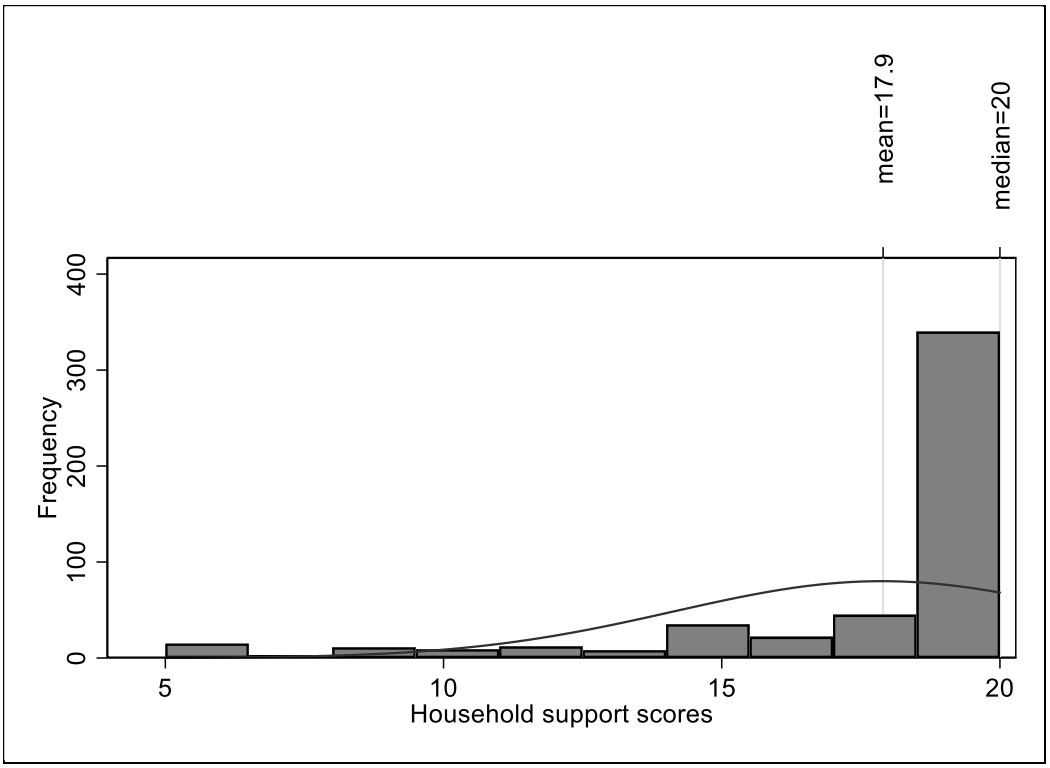
Supplementary material 1: Histograms, median, mean and Cronbach for psychosocial variables

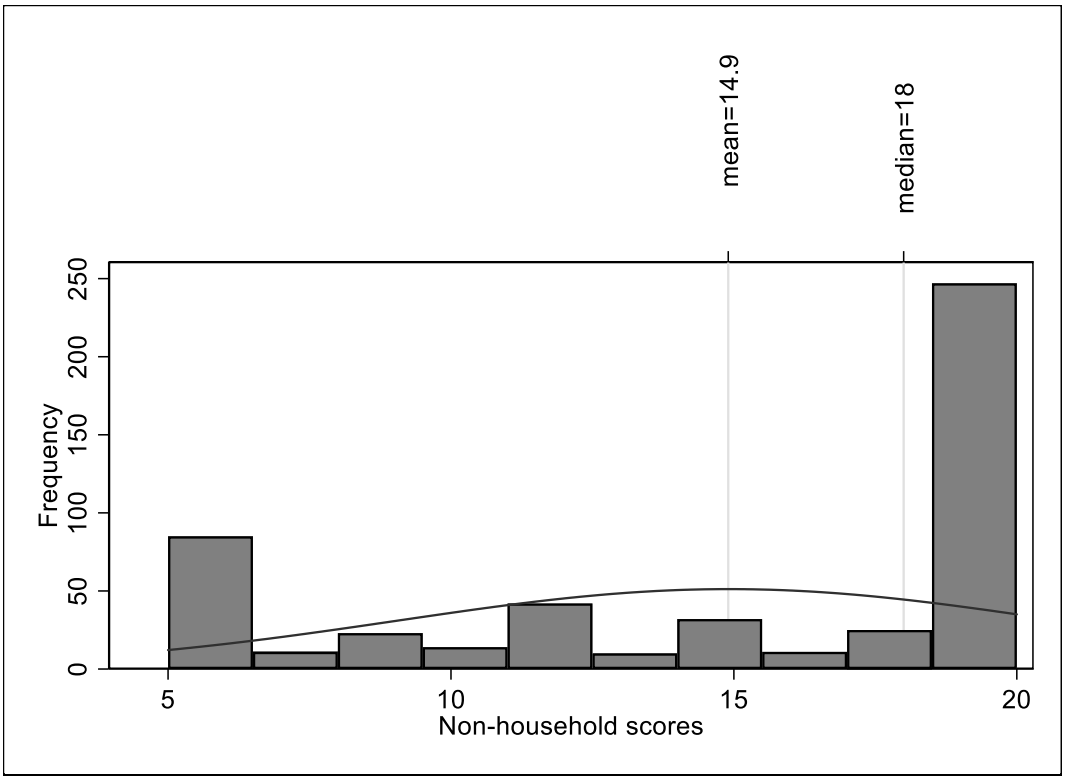


Supplementary graph 1: Distribution of adherence self-efficacy scores for the ITREMA participants,

Cronbach's alpha = 0.87

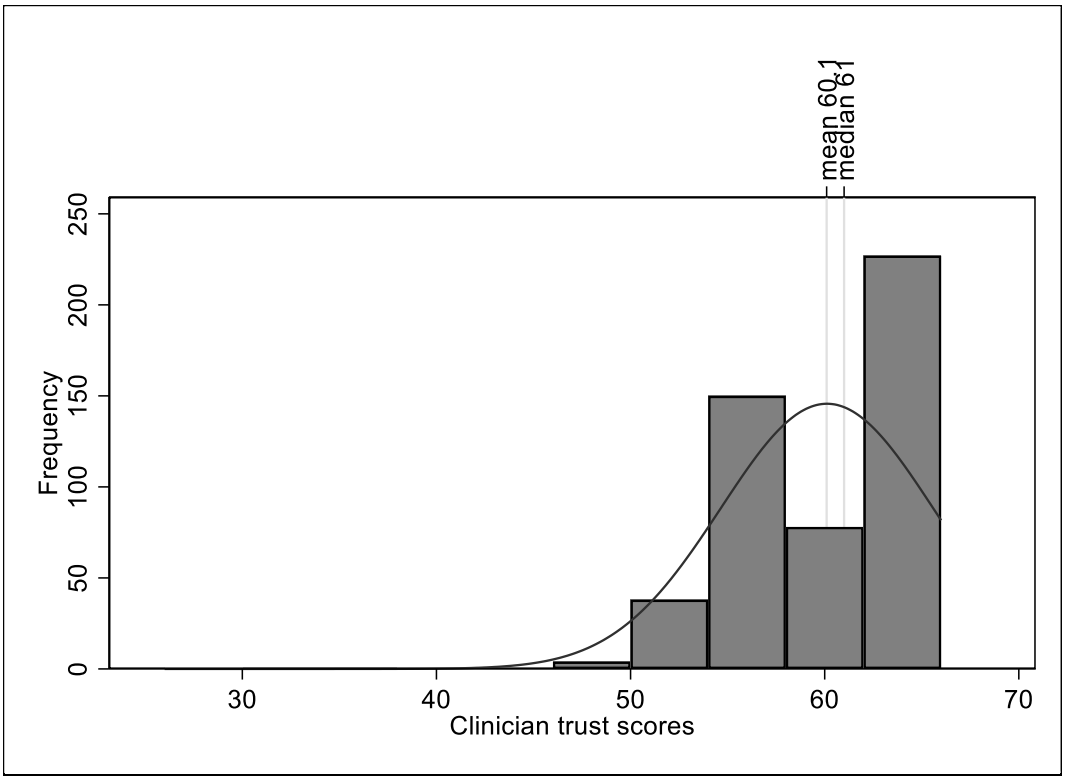


Supplementary graph 2: Distribution of household support scores for the ITREMA participants.
Cronbach's alpha = 0.92



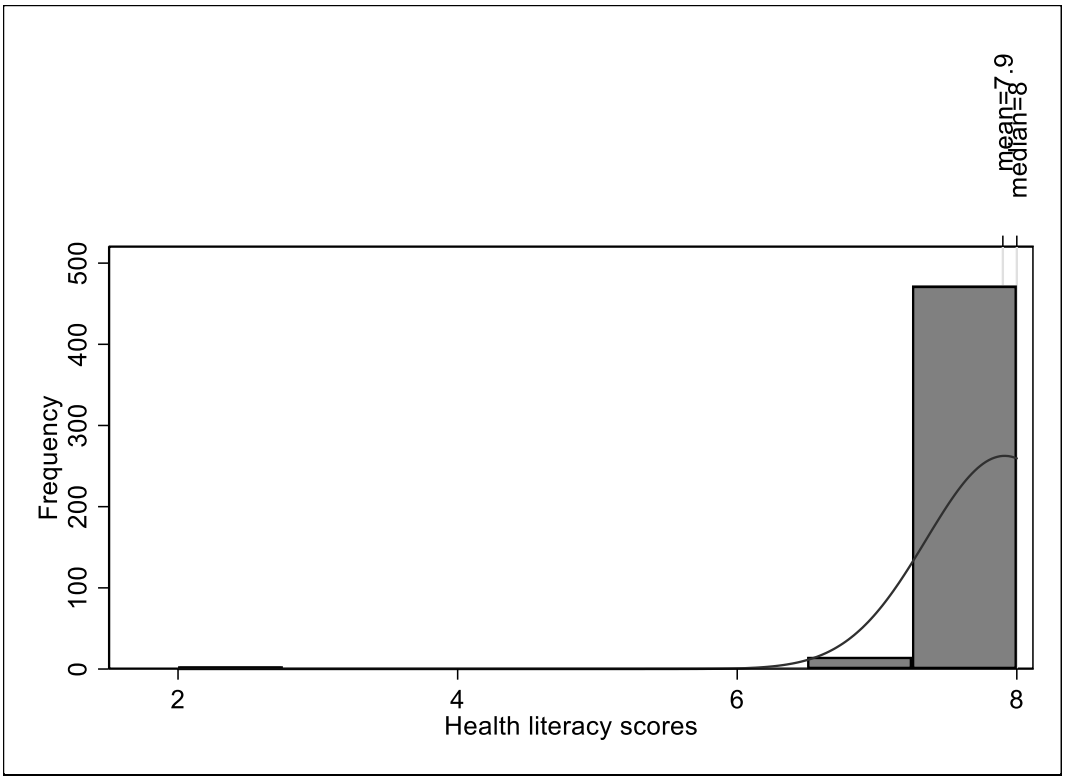
Supplementary graph 3: Distribution of non-household support scores for the ITREMA participants.

Cronbach's alpha = 0.96

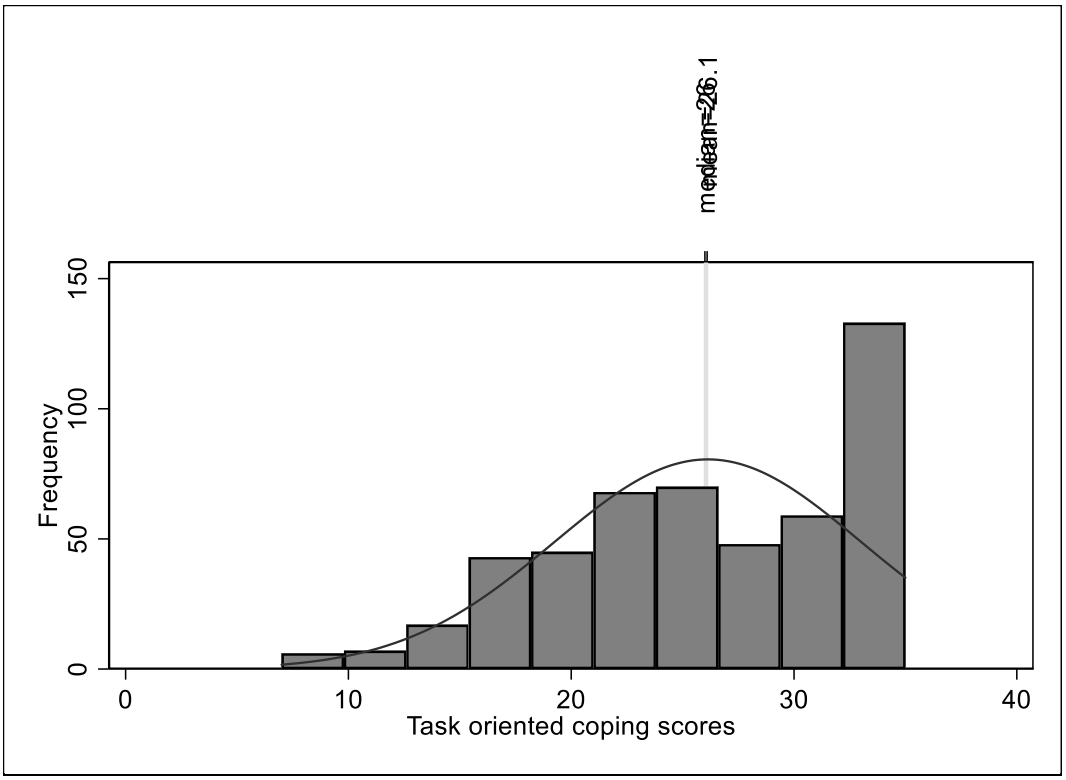


Supplementary graph 4: Distribution of clinician trust scores for the ITREMA participants

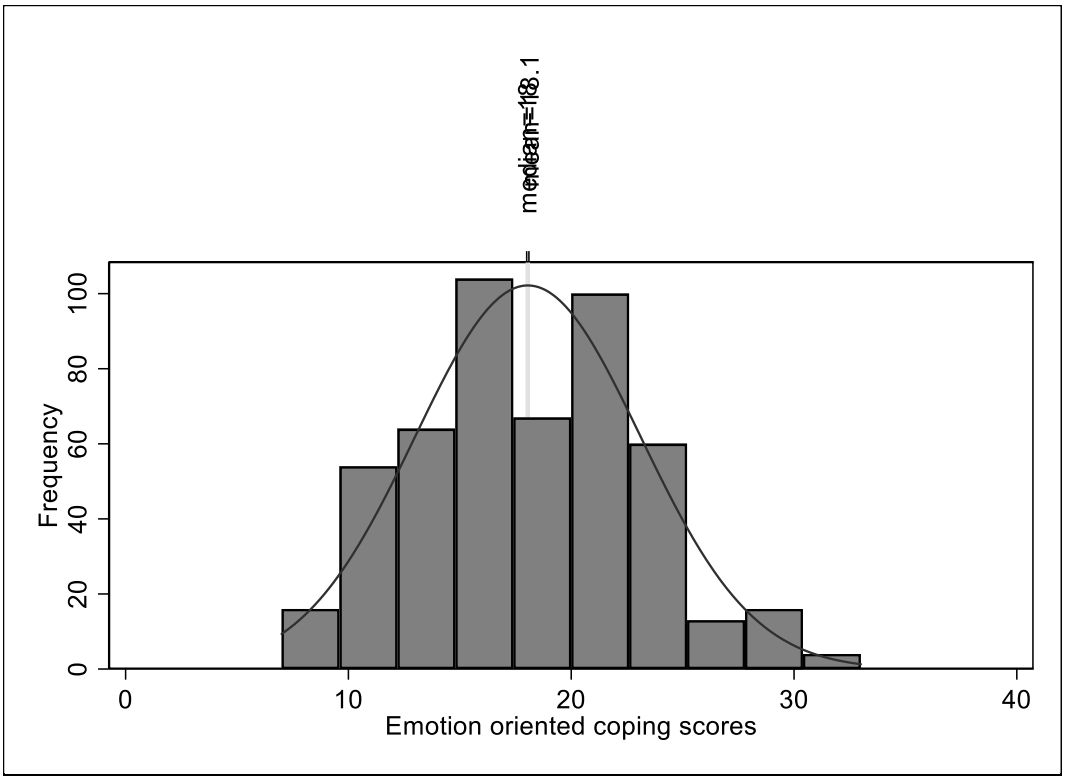
Cronbach's alpha = 0.72



Supplementary graph 5: Distribution of health literacy scores for the ITREMA participants.
Cronbach's alpha = 0.82

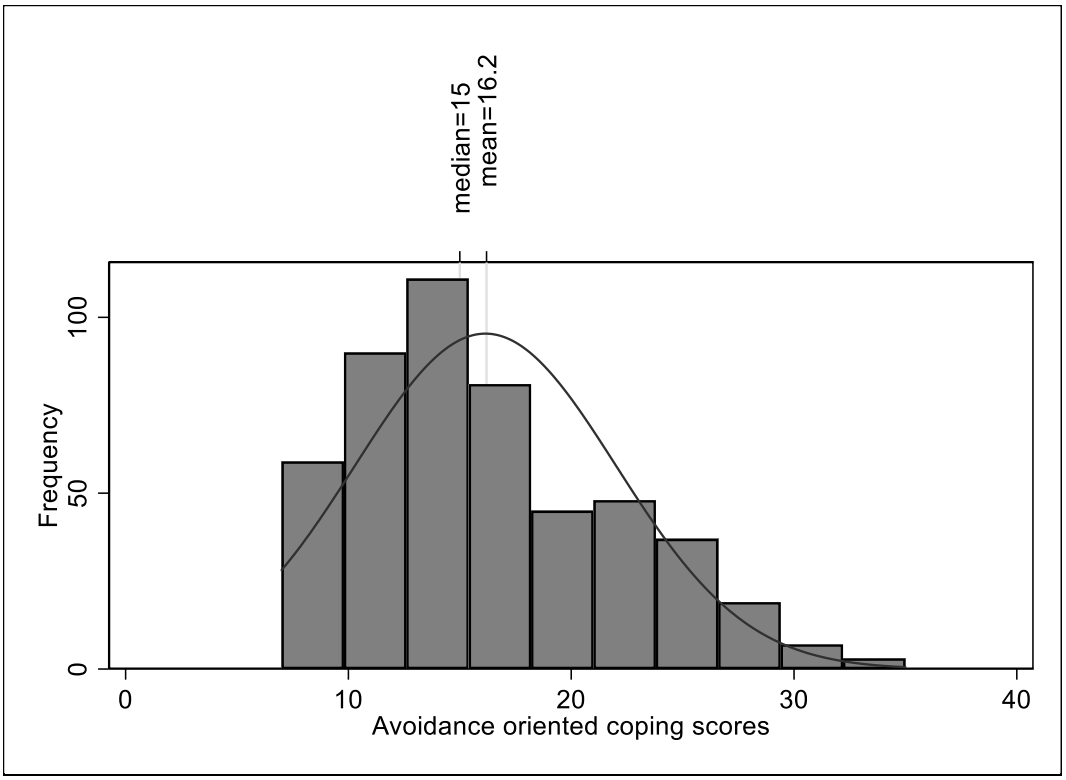


Supplementary graph 6: Distribution of task oriented coping scores for the ITREMA participants.
Cronbach's alpha = 0.88



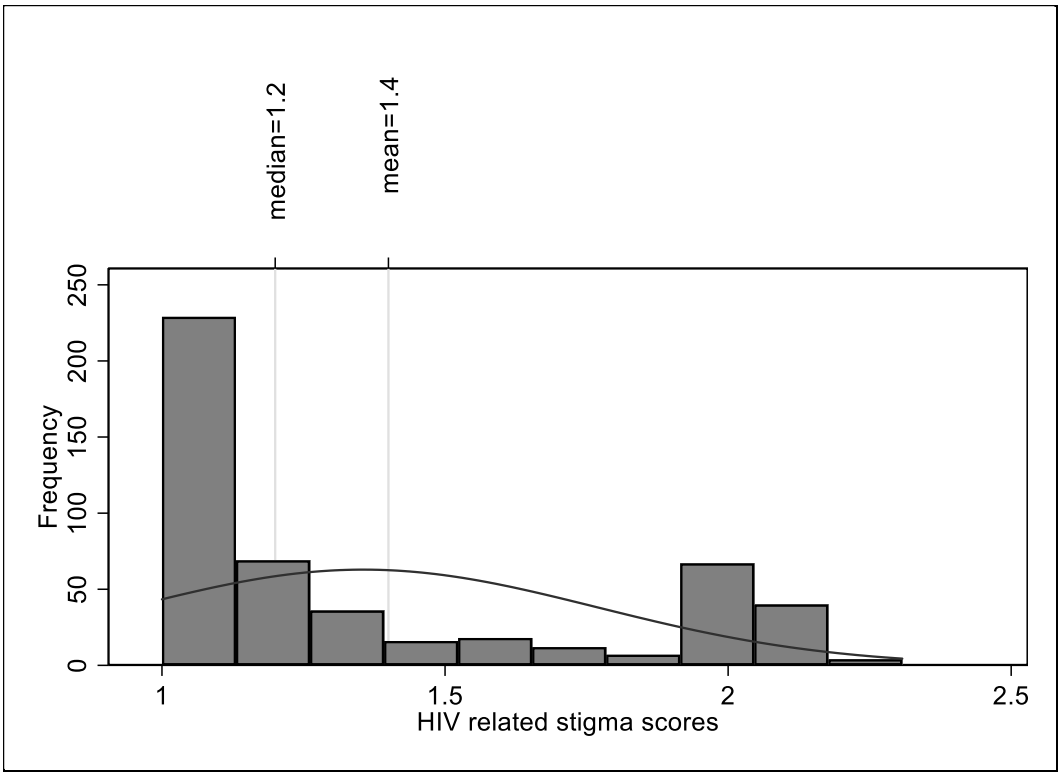
Supplementary graph 7: Distribution of emotion oriented coping scores for the ITREMA participants.

Cronbach's alpha = 0.74

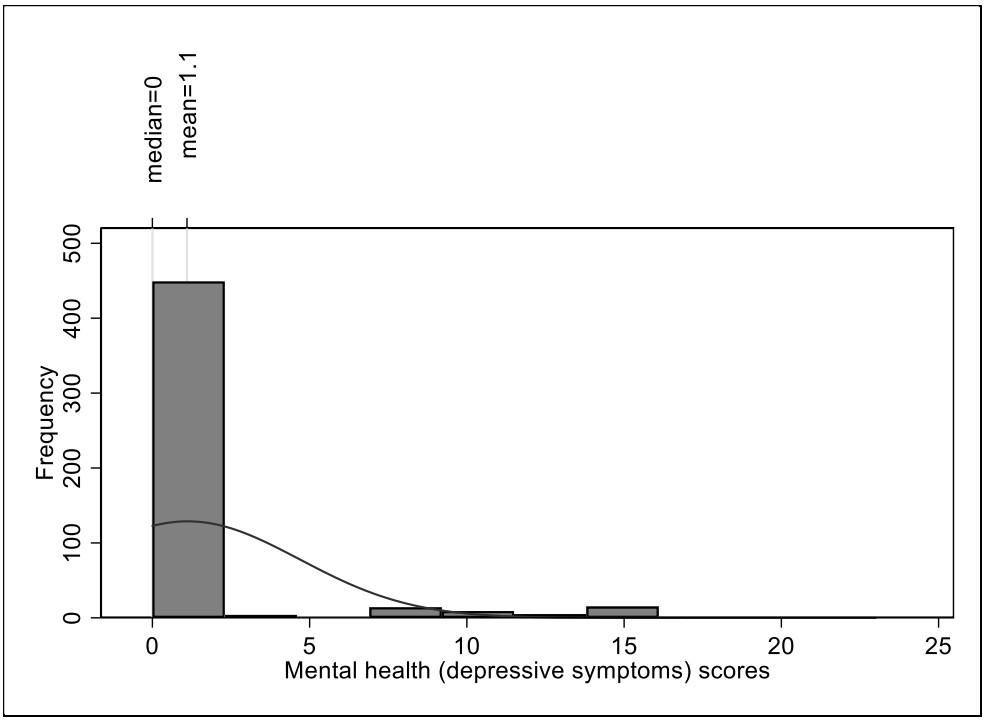


Supplementary graph 8: Distribution of avoidance oriented coping scores for the ITREMA participants.

Cronbach's alpha = 0.74



Supplementary graph 9: Distribution of HIV related stigma scores for the ITREMA participants.
Cronbach's alpha = 0.87



Supplementary graph 10: Distribution of Mental health (depressive symptoms) scores for the ITREMA participants.

Cronbach's alpha = 0.78

Supplementary material 2: Univariate analyses of sociodemographic and psychosocial factors associated with self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

Sociodemographic characteristics		Self-reported adherence difficulties			Pill count <95%			Virological failure (≥1000 copies/ml)		
		Unadjusted Odds Ratio (95% CI)	p-value	z value	Unadjusted Odds Ratio (95% CI)	p-value	z value	Unadjusted Odds Ratio (95% CI)	p-value	z value
Gender (male)	150 (29.9%)	1.74 (1.15-2.63)	0.008	2.64	1.61 (1.07-2.44)	0.023	2.27	1.97 (1.15-3.35)	0.013	2.49
Age (median)	42.0 years [36.0-49.0 years]	0.994 (0.997-1.011)	0.521	-0.64	0.99 (0.97-1.01)	0.249	-1.15	0.98 (0.96-1.01)	0.188	-1.32
Relationship status (in a relationship)	294 (58.7)	1.05 (0.72-1.52)	0.817	0.23	1.05 (0.71-1.55)	0.820	0.23	0.79 (0.47-1.34)	0.385	-0.87
Education (primary vs secondary/tertiary level)	470 (93.8)	0.76 (0.36-1.60)	0.469	-0.72	0.77 (0.34-1.72)	0.525	-0.63	0.82 (0.28-2.44)	0.724	-0.35
Employment (unemployed)	256 (51.1)	1.03 (0.72-1.49)	0.865	0.17	1.21 (0.82-1.77)	0.335	0.96	1.46 (0.86-2.47)	0.157	1.41
Household income median (ZAR) (median)	R1600.00 [R700.00-R4200.00	1.00 (0.95-1.03)	0.851	-0.19	0.94 (0.89-0.99)	0.021	-2.31	0.98 (0.92-1.05)	0.629	-0.48
Social grants										
Child related grant	113 (22.6)	1	-	-	1	-	-	1	-	-
Disability grant	16 (3.2)	1.05 (0.34-3.25)	0.090	0.929	0.60 (0.16-2.29)	0.451	-0.75	1.50 (0.37-6.10)	0.571	0.57
No grants	257 (51.3)	0.87 (0.54-1.38)	0.547	-0.60	1.34 (0.82-2.19)	0.579	1.16	0.75 (0.40-1.41)	0.373	-0.89
Old-age related grant	90 (18.0)	0.79 (0.44-1.41)	0.424	-0.80	1.28 (0.70-2.35)	0.428	0.79	0.63 (0.27-1.44)	0.270	-1.10
Other grants	25 (5.0)	1.05 (0.41-2.72)	0.916	0.11	0.88 (0.31-2.46)	0.800	-0.25	1.61 (0.51-5.03)	0.415	0.81
Number of people living together (median)	5 people [3-7 people]	0.95 (0.89-1.02)	0.158	-1.41	0.93 (0.87-1.00)	0.054	-1.93	1.05 (0.96-1.15)	0.295	1.05
Food insecurity (in the last 30 days)	41 (8.2)	0.88 (0.44-1.73)	0.702	-0.38	1.51 (0.76-3.01)	0.238	1.18	2.01 (0.90-4.50)	0.091	1.69
Psychosocial characteristics										
Adherence self-efficacy (adequate)	472 (94.2)	0.45 (0.18-1.10)	0.080	-1.75	0.53 (0.23-1.20)	0.129	-1.52	1.70 (0.38-7.49)	0.485	0.70
Health literacy (high)	487 (98.8)	0.56 (0.10-3.10)	0.508	-0.66	0.27 (0.05-1.47)	0.129	-1.52	0.92 (0.11-8.02)	0.941	-0.07
Clinician trust (high)	497 (99.6)	1	-	-	1	-	-	1	-	-
Household support	434 (86.8)	1.16 (0.67-1.99)	0.597	0.53	1.44 (0.79-2.62)	0.232	1.20	0.91 (0.44-1.91)	0.812	-0.24

Non-household family support (good)	305 (60.9)	1.02 (0.70-1.48)	0.923	0.10	1.11 (0.75-1.65)	0.593	0.53	0.94 (0.56-1.60)	0.829	-0.22
Coping strategy scores										
Task-oriented coping (median)	26 (21-33)	0.97 (0.95-1.00)	0.058	-1.89	0.97 (0.94-1.00)	0.026	-2.23	0.96 (0.93-1.00)	0.052	-1.94
Emotion oriented coping (median)	18 (14-22)	0.97 (0.94-1.01)	0.099	-1.65	0.99 (0.95-1.03)	0.513	-0.65	0.95 (0.90-1.00)	0.060	-1.88
Avoidance oriented coping (median)	15 (12-20)	1.00 (0.97-1.03)	0.979	0.03	1.00 (0.96-1.03)	0.851	-0.19	0.97 (0.93-1.02)	0.256	-1.14
HIV-related (internalized) stigma	258 (51.8)	1.37 (0.95-1.98)	0.096	1.66	1.45 (0.98-2.13)	0.061	1.87	1.57 (0.93-2.66)	0.094	1.67
Mental Health (moderate or severe depressive symptoms)	31 (6.2)	1.84 (0.81-4.19)	0.146	1.45	2.07 (0.95-4.53)	0.067	1.83	3.14 (1.34-7.38)	0.009	2.63

Supplementary material 3: Sensitivity analysis: Multivariable analyses of sociodemographic and psychosocial factors associated with of self-reported ART adherence difficulties, suboptimal adherence as indicated by pill count <95% and virological failure among participants in the ITREMA Trial

Variable	Self-reported non-adherence		
	Adjusted Odds Ratio (95% CI)	p-value	z score
Gender			
Female	Ref		
Male	1.77 (1.16-2.70)	**0.008**	2.67
Adherence self-efficacy	0.88 (0.76-1.02)	0.099	-1.20
Task orientated coping	0.99 (0.96-1.02)	0.433	-1.16
Emotion orientated coping	0.98 (0.94-1.02)	0.301	-1.19
HIV reported stigma	1.07 (0.61-1.89)	0.812	0.84
Variable	**Pill count <95**		
	Adjusted Odds Ratio (95% CI)	**p-value**	
Gender			
Female	Ref	-	
Male	1.59 (1.02-2.46)	**0.040**	2.04
Household income	0.93 (0.88-0.99)	**0.019**	-2.33
Number of people living together category	0.93 (0.87-1.01)	0.080	-1.77
Adherence self-efficacy	0.89 (0.78-1.01)	0.072	-0.64
Health literacy	0.65 (0.43-0.96)	**0.031**	-1.65
Household family support	1.09 (1.02-1.16)	**0.008**	1.28
Task orientated coping	0.87 (0.56-1.35)	0.543	-2.10
Variable	**Virological failure (≥1000 copies/ml)**		
	Adjusted Odds Ratio (95% CI)	**p-value**	
Gender			
Female	Ref	-	
Male	1.97 (1.14-3.41)	**0.016**	2.43
Food insecurity in the last 30 days			
No reported food insecurity in the last 30 days	Ref		
Reported food insecurity in the last 30 days	1.64 (0.69-3.91)	0.266	1.28
Adherence self-efficacy	0.99 (0.80-1.22)	0.898	1.27
Clinician trust	0.94 (0.88-1.01)	0.099	-1.73
Coping strategy scores			
Task orientated coping	0.98 (0.94-1.02)	0.386	-1.07
Emotion orientated coping	0.95 (0.90-1.01)	0.100	-1.67
HIV reported stigma	0.83 (0.34-2.05)	0.688	-0.20
Moderate or severe depressive symptoms	1.08 (1.01-1.15)	**0.024**	2.26

Supplementary material 4: Sensitivity analysis for self-reported adherence: Association of socio-demographic and psycho-social characteristics with ART adherence

	Overall sample, n (%) or median [IQR]	Self-reported non-adherence (n=458)					
		Poor self-reported adherence (n=235, 51.3%)	%	Good self-reported adherence (n=223, 48.7%)	%	p-value	Chi-square value/ t value
Sociodemographic characteristics							
Gender (male)	150 (29.9%)	81	34.5	53	23.8	**0.012**	6.3308
Age (median)	42.0 years [36.0-49.0 years]	42 (37-49)	-	43 (36-50)	-	0.735	0.3393
Age (category)							
<35 years	114 (22.8)	49	20.85	46	20.63		
35-49 years	257 (51.3)	128	54.47	113	50.67		
>50 years	130 (26.0)	58	24.68	64	28.70		
Relationship status (in a relationship)	294 (58.7)	139	59.15	132	59.19	0.992	0.0001
Education (secondary/tertiary)	408 (81.4)	197	81.1	176	81.9	0.828	0.8176
Employment (unemployed)	256 (51.1)	120	51.06	112	50.22	0.857	0.0323
Household income median (per 1000.00 ZAR) (median)	R1600.00 [R700.00-R4200.00]	1500 (700-4000)		1600 (700-4300)		0.969	-0.0388
Household income per month (category)							
<3,500 ZAR	346 (69.1)	167	71.06	152	68.16		
3,500-10,000 ZAR	124 (24.8)	52	22.13	61	27.35		
>10,000 ZAR	31 (6.2)	16	6.81	10	4.48		
Number of people living together (median)	5 people [3-7 people]	5 (3-7)		5 (3-7)		**0.095**	1.6771
Number of people living together (category)							
1-2	58 (11.6)	29	12.34	22	9.87		
3-5	233 (46.5)	111	47.23	102	45.74		
Above 5	210 (41.9)	95	40.43	99	44.39		
Food insecurity (in the last 30 days)	41 (8.2)	18	7.66	18	8.07	0.870	0.0268
Psychosocial characteristics							
Adherence self-efficacy (adequate)	472 (94.2)	218	92.77	216	96.86	**0.056**	3.8641
Health literacy (high)	487 (98.8)	228	98.28	218	99.09	0.457	0.5727
Clinician trust (high)	499 (99.6)	235	100.0	222	99.6	0.487	1.0564
Household support (good)	434 (86.8)	205	87.23	192	86.49	0.813	0.0559
Non-household family support (good)	305 (60.9)	143	60.85	135	60.54	0.945	0.0047
Coping strategy scores							
Task-oriented coping (median)	26 (21-33)	26 (20-32)		28 (21-33)		**0.029**	2.2013
Emotion oriented coping (median)	18 (14-22)	17 (14-21)		18 (14-22)		**0.071**	1.8129
Avoidance oriented coping (median)	15 (12-20)	16 (12-20)		15 (12-20)		0.653	-0.4481
HIV-related (internalized) stigma	258 (51.8)	129	55.13	103	46.40	**0.063**	3.4754
Mental Health (Moderate or severe depressive symptoms)	31 (6.2)	16	6.84	11	4.93	0.390	0.7453

Supplementary material 4a: Sensitivity analyses: Logistic regression analysis between self-reported non-adherence and socio-demographic and pyscho-social characteristics of ART participants in the ITREMA trial.

Variable	Self-reported adherence difficulties		
	Adjusted Odds Ratio (95% CI)	p-value	z value
Gender			
Female	Ref		
Male	1.69 (1.10-2.55)	**0.017**	**2.40**
Number of people living together (median)	0.95 (0.89-1.02)	0.147	-1.45
Adherence self-efficacy			
Inadequate adherence self-efficacy	Ref		
Adequate adherence self-efficacy	0.55 (0.22-1.39)	0.205	-1.27
Coping strategy scores (CISS)			
Task-oriented coping	0.98 (0.95-1.01)	0.106	-1.62
Emotion-oriented coping	0.97 (0.94-1.01)	0.162	-1.40
HIV related stigma			
No reported stigma	Ref		
Reported stigma	1.17 (0.78-1.74)	0.443	0.77

CHAPTER 6

Understanding adherence in virally suppressed and unsuppressed human immunodeficiency virus-positive urban patients on second-line antiretroviral treatment

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ABSTRACT

Background: Understanding antiretroviral therapy (ART) adherence may assist in designing effective support interventions.

Objectives: This study elicited perspectives on how to promote treatment adherence from virologically suppressed and unsuppressed patients receiving second-line ART.

Methods: This was a cross-sectional study conducted with randomly selected patients active on second-line ART, from five public health facilities in the Johannesburg inner city. Data were collected on demographics, clinical information, participant's experiences and ART knowledge. Virological failure was defined as exceeding 1000 copies/mL.

Results: The study sample comprised 149 participants; of which 47.7% (*n* = 71) were virally unsuppressed and 69.1% (*n* = 103) were women; the median age of the participants was 42 years (interquartile range [IQR] 36–47 years). Experiencing medication-related difficulties in taking second-line ART ($p = 0.003$), finding second-line regimen more difficult to take than a first-line regimen ($p = 0.001$) and experiencing side effects ($p < 0.001$) were all subjective predictors of virological failure. Participants' recommendations for improving adherence included the introduction of a single tablet regimen (31.6%, *n* = 55), reducing the dosage to once daily (26.4%, *n* = 46) and reducing the pill size for second-line regimen (4.0%, *n* = 7).

Conclusion: The results of this study highlight the importance of improving patients' knowledge about adherence and motivation to continue ART use despite the persistence of side effects and difficulties with taking medication.

Keywords: adherence; viral load suppression; virological failure; antiretroviral therapy; South Africa

INTRODUCTION

The World Health Organization (WHO) defines adherence as the degree to which a patient is able to follow a treatment plan and take medication at prescribed times [1].

Factors that affect treatment adherence include changes in daily routines, forgetting to take medication, side effects, depression, being away from home, comorbidity, lack of knowledge and desire to take treatment [2-4]. In addition, patients experiencing financial constraints, social issues such as the fear of disclosure and lack of understanding of treatment benefits are more prone to non-adherence to treatment and illnesses [5,6]. Some studies have reported disclosure and relationship with the person being disclosed to as predictors of adherence [7,8].

The South African government's adherence promotion strategies include routine viral load monitoring, adherence counselling, pill counting, adherence clubs and routine completion of clinical stationery [9-11]. Despite all these antiretroviral therapies (ART) adherence strategies being implemented, treatment failure amongst patients on first- and second-line ART remains an issue [12]. Lapses in ART medication adherence can lead to viral rebound with ongoing immunosuppression and viral resistance [1,13,14]. However, not much is understood about the perspectives of patients regarding adherence challenges [15,16].

Therefore, this study sought to describe and obtain perspectives on treatment adherence from two separate groups of patients on second-line therapy, those who were suppressed and those who were not, to understand treatment-taking behaviour.

MATERIALS AND METHODS

Study design and setting

This was a cross-sectional study conducted between July and August 2018 in a sub-population of patients receiving second-line ART at the end of June 2018. Five public health facilities in inner-city Johannesburg (two hospitals, one community health centre and two primary healthcare clinics) were included in the study.

Study population

The study population comprised patients aged 18 years and older who were on second-line ART for at least 1 month or longer.

Data collection

Sample selection and recruitment

We randomly sampled 10% of the population of 1500 eligible patients. The total number of active patients on second-line treatment per facility was divided by the total sample size (n = 150) to determine the interval that needed to be used to select the eligible patients. Using this formula, every nth (different for each facility) record from the register or list of active patients on second-line treatment in each facility was selected and recruited to the study until the facility sample size

was reached. Once the eligible patients were identified, they were invited to participate in the study in one of the two ways: telephonically or in facility recruitment where researchers met them at the facility during their scheduled clinic visit. For the patients who refused to participate in the study, the next *n*th patient was recruited.

Data collection, tool and variables

A pretested semi-structured questionnaire was used, which consisted of five sections: (1) demographic data, (2) comorbidity information, (3) human immunodeficiency virus (HIV) diagnosis and care information, (4) experiences on the first-line regimen and adherence and (5) experiences on second-line regimen and adherence. Information collected included demographic information (facility name, sex, age, relationship status, employment status and education level), comorbidity information, experiences on both first- and second-line treatment, disclosure information, duration on ART, reasons for starting ART, side effects, self-reported treatment interruptions, challenges with taking second-line treatment, treatment supporter information and insights into how adherence could be improved.

Questionnaire administration

Data were collected by the principal investigator and a trained research assistant. The interviews were conducted in English as it was the most commonly spoken language in the study setting and all participants could speak it.

Data entry, cleaning and analysis

Data were captured into REDCap immediately after interviews were conducted. The research team conducted data clean-up by running data quality checks in REDCap and STATA (quantitative data). For the closed-ended questions, we assessed the association between outcome variables and selected socio-demographic and health-related characteristics. Pearson's chi-squared test was used to assess trend associations between categorical variables. Continuous data were summarised and analysed using the median and interquartile ranges (IQRs). Logistic and multiple logistic regression models (bivariate and multivariate logistic regression) were built for key outcome variables, such as viral load, difficulties in taking second-line regimen and side effects, to identify independent predictors. We reported unadjusted and adjusted odds ratios (ORs), 95% confidence interval (CI) and *p*-values – *p*-values that were less than 0.05 were considered significant. Open-ended questions were analysed using qualitative data analysis methods. Data were coded and thematic analysis was performed. Where appropriate, quotations have been included to support the reported results.

Ethical consideration

Ethical approval to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (ethical clearance number: M170691). Approval was also granted by the Johannesburg Health District (DRC Ref No. 2017-08-003 and NHRD Ref No. GP_201708_030). Participants were informed that participation in the study was voluntary, and that refusal would not affect their relationship with their healthcare provider or facility. All patients who agreed to participate in the study signed an informed consent form. To ensure confidentiality, there

were no linkages between the data collected in the questionnaire and the patients' clinic information. Participants were reimbursed for their travel.

RESULTS

Sample characteristics

A total of 150 out of 1500 active patients on second-line ART across the five public health facilities were interviewed (69.1%, *n* = 103 women). During the quality checking processes, we found that one of the participants was younger than 18 years and was subsequently omitted from the analysis. The median age of the participants was 42 years (IQR 36–47 years). Most of the participants were single (38.1%, *n* = 57); 30.2% (*n* = 45) participants were married. Nearly two-thirds of the participants were born in South Africa (61.1%, *n* = 91), whilst almost one-third of the participants were born in Zimbabwe (32.9%, *n* = 49). The majority (87.2%, *n* = 130) of participants had completed at least their secondary or high school-level education. A minority (8.1%, *n* = 12) of participants had completed tertiary qualifications; 4.7% (*n* = 7) participants had never attended a school. Of the total participants, 45.6% (*n* = 68) were unemployed. The majority of participants were identified as Christian (87.9%, *n* = 131). Hypertension (65.1%, *n* = 28/43), diabetes (9.3%, *n* = 4/43) and hypercholesterolaemia (9.3%, *n* = 4/43) were the most common concomitant conditions reported by the participants. The average distance travelled to reach a health facility was 5 km (IQR: 2 km – 15 km), with 57.7% (*n* = 86) participants travelling 5 km or less to reach the health facility.

Socio-demographic and virological status

Table 1 shows the socio-demographic characteristics disaggregated by virological status. Nearly half (47.7%, *n* = 71) of the participants interviewed had virological failure (VLF), with women accounting for 73.2% (*n* = 52). With regard to age, of the total unsuppressed participants, 39.4% (*n* = 28) were between 30 and 39 years. Of the participants with virological suppression (VLS), 29.5% (*n* = 23) had comorbidity compared to VLF participants (28.2%, *n* = 20).

Table 1: Socio-demographic and treatment-taking characteristics disaggregated by virological status of second-line participants in five health facilities in the Johannesburg inner city

Variable Total patient/participants recruited	Total n (%) N=149 (100)	Virologic Status		p-value
		Suppressed (VLS), n (%) 78 (52.3)	Unsuppressed (VLF), n (%) 71 (47.7)	
Facility				
Charlotte Maxeke Johannesburg Academic Hospital	32 (21.5)	19 (24.4)	13 (18.3)	
Hillbrow Community Health Centre	86 (57.7)	43 (55.1)	43 (60.6)	
South Rand Hospital	21 (14.1)	16 (20.5)	5 (7.0)	**0.001**
Primary Healthcare Clinics (Malvern Clinic Yeoville Clinic[1])	10 (6.7)	0	10 (14.1)	
Gender				
Female	103 (69.1)	51 (65.4)	52 (73.2)	0.300
Male	46 (30.9)	27 (34.6)	19 (26.8)	
Age, Median (42, IQR: 35-47)				
< 30	11 (7.4)	3 (3.9	8 (11.3)	
30-39	52 (34.9)	24 (30.8)	28 (39.4)	0.152
40-45	43 (28.9)	25 (32.1)	18 (25.4)	
45+	43 (28.9)	26 (33.3)	17 (23.9)	
Country of birth				
South Africa	91 (61.1)	42 (53.9)	49 (69.0)	
Zimbabwe	49 (32.9)	32 (41.0)	17 (23.9)	0.085
Other	9 (6.0)	4 (5.1)	5 (7.0)	
Home language				
Zulu	62 (41.6)	32 (41.0)	30 (42.3)	
Ndebele	36 (24.2)	21 (26.9)	15 (21.1)	
Xhosa	12 (8.1)	6 (7.7)	6 (8.5)	0.893
Sotho	12 (8.1)	5 (6.4)	7 (9.9	
Other	27 (18.1)	14 (18.0)	13 (18.3)	
Relationship status				
Married	45 (30.2)	28 (35.9)	17 (23.9)	
Cohabiting	38 (25.5)	16 (20.5)	22 (31.0	
Single	57 (38.3)	30 (38.5)	27 (38.0)	0.310
Other	9 (6.0)	4 (5.1)	5 (7.0)	
Highest education level completed				
Never went to school	7 (4.7)	4 (5.1)	3 (4.2)	
Secondary/High School	130 (87.2)	69 (88.5)	61 (85.9)	0.737
Tertiary	12 (8.1)	5 (6.4)	7 (9.9)	
Employment status				
Employed	65 (43.6)	37 (47.4)	28 (39.4)	
Unemployed	68 (45.6)	33 (42.3)	35 (49.3)	0.613
Other[2]	16 (10.7)	8 (10.3)	8 (11.3)	
Religion				
Christianity	131 (87.9)	67 (85.9)	64 (90.1)	
Ancestral/traditional	8 (5.4)	7 (9.0)	1 (1.4)	0.098
Other	10 (6.7)	4 (5.1)	6 (8.5)	
Comorbidity				
Yes	43 (28.9)	23 (29.5)	20 (28.2)	0.859
No	106 (71.1)	55 (70.5)	51 (71.8)	

[1] Second-line patients are often managed at a higher level of facility.

[2] People not looking for employment at that time for example students and housewives

Variable Total patient/participants recruited	Total n (%) N=149 (100)	Virologic Status		p-value
		Suppressed (VLS), n (%) 78 (52.3)	Unsuppressed (VLF), n (%) 71 (47.7)	
Distance travelled to the facility, Median (5, IQR: 2-15)				
5 km or less	86 (57.7)	45 (57.7)	41 (57.8)	0.764
6-10 km	21 (14.1)	12 (15.4)	9 (12.7)	
11-20 km	23 (15.4)	10 (12.8)	13 (18.3)	
Above 20 km	19 (12.8)	11 (14.1)	8 (11.3)	
Who was the first person to disclose your HIV status to?				
Partner	70 (47.0)	33 (42.3)	37 (52.1)	0.228
Family/relative member	77 (51.7)	43 (55.1)	34 (47.9)	
Friend	2 (1.3)	2 (2.6)	0	
How long did it take you to disclose your HIV status?				
Within one week	94 (63.1)	48 (61.5)	46 (64.8)	0.306
1-2 weeks	8 (5.4)	4 (5.1)	4 (5.6)	
3-4 weeks	4 (2.7)	4 (5.1)	0	
More than four weeks	42 (28.2)	22 (28.2)	20 (28.2)	
Never disclosed	1 (0.7%)	0	1 (1.4)	
Do you have anyone supporting you take your ARVs currently?				
Yes	118 (79.2)	61 (78.2)	57 (80.3)	0.755
No	31 (20.8)	17 (21.8)	14 (19.7)	
Do you feel the current regimen is difficult to take compared to the previous regimen(s)?				
Yes	78 (52.3)	31 (39.7)	47 (66.2)	**0.001**
No	71 (47.7)	47 (60.3)	24 (33.8)	
Have you been experiencing difficulties taking the current regimen?				
Yes	57 (38.3)	21 (26.9)	36 (50.7)	**0.003**
No	92 (61.7)	57 (73.1)	35 (49.3)	
Have you experienced any side effects since you switched regimens/drugs?				
Yes	71 (47.7)	26 (33.3)	45 (63.4)	**<0.001**
No	78 (52.3)	52 (66.7)	26 (36.6)	
Have you ever stopped taking the current regimen for over a month?				
Yes	5 (3.4)	3 (3.8)	2 (2.8)	0.728
No	144 (96.6)	75 (96.2)	69 (97.2)	
Have you ever felt like stopping the current regimen/drugs completely?				
Yes	15 (10.1)	7 (9.0)	8 (11.3)	0.642
No	134 (89.9)	71 (91.0)	63 (88.7)	
Have you ever felt like switching current regimen/drugs for something else?				
Yes	58 (38.9)	26 (33.3)	32 (45.1)	0.142
No	91 (61.1)	52 (66.7)	39 (54.9)	

Abbreviations: N, number; VLS, virological suppression; n, number; VLF, virological failure; p, probability value; IQR, interquartile range; km, kilometre; ARVs, antiretrovirals; HIV, human immunodeficiency virus. **Bold values indicates significant values at p<0.05.**

Disclosure, treatment support and virological status

Almost all the participants' first disclosure of their HIV status was to a partner or relative (98.7%, *n* = 147 combined). More VLS participants (55.1%, *n* = 43) disclosed about their HIV status to a family member first, whilst most VLF participants (52.1%, *n* = 37) chose to disclose to their partners first. Almost no disclosure to friends was reported. Disclosure did not show any statistical significance. Participants typically (63.1%, *n* = 94) disclosed within 1 week after HIV diagnoses, with more VLF participants reporting early disclosure than VLS participants (64.8%, *n* = 46 vs. 61.5%, *n* = 48). Most participants (79.2%, *n* = 118) had treatment supporters (VLF = 80.3%, *n* = 57; VLS = 78.2%, *n* = 61). Whilst 10.1% (*n* = 15) of participants felt like stopping treatment completely at some point, only 3.4% (*n* = 5) stopped treatment for longer than 1 month, more in VLS participants, although this was not statistically significant.

Factors of virological failure and adherence

Overall, there were more participants (52.3%, *n* = 78) who felt that taking a second-line regimen was difficult compared to the first-line regimen, with the VLF group (66.2%, *n* = 47, *p* = 0.001) predominantly reporting this challenge. Generally, 38.3% (*n* = 57/149) experienced difficulties in taking the second-line regimen (*p* = 0.003). Of these, about two-thirds (63.2%, *n* = 36) were VLF participants (*p* = 0.003). Just under half (47.7%, *n* = 71/149) of the participants experienced side effects whilst taking their second-line regimen, and of these, 63.4% (*n* = 45) were VLF participants (*p* < 0.001).

Table 2 presents results from both bivariate and multivariate logistic regression analysis. No association was detected between VLF and relationship status in bivariate analysis. However, in multivariate analysis, participants who cohabit were three times more likely to have a VLF than those who are married (adjusted odds ratios [AORs] 3.1, 95% CI = 1.1– 8.9; *p* = 0.035). Unemployed participants were two and a half times more likely to have treatment-related side effects compared to employed participants (AOR 2.5, 95% CI = 1.1– 5.7; *p* = 0.023). Results for age did not show any statistical significance but older people were less likely to be unsuppressed.

Table 2: Logistic regression analysis between outcome variables and socio-demographic characteristics of second-line participants in Johannesburg inner-city

	Virological failure				Experiencing difficulties taking second-line regimen				Feeling that second-line regimen is difficult to take				Side effects			
Variable	UOR	P	AOR	p	UOR	p	AOR	p	UOR	p	AOR	p	UOR	p	AOR	p
Facility																
CMJAH	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
HCHC	1.3 (0.6-3.1)	0.460	1.6 (0.6-4.4)	0.475	2.0 (0.8- 4.7)	0.113	2.0 (0.7- 5.7)	0.185	2.4 (1.1-5.6)	0.037	1.7 (0.7-4.8)	0.246	2.1 (0.9-4.8)	0.080	1.8 (0.7-4.9)	0.233
SRH	0.4 (0.1-1.4)	0.168	0.4 (0.1- 1.4)	0.136	0.3 (0.1- 1.5)	0.170	0.4 (0.1- 2.1)	0.301	0.7 (0.2-2.2)	0.503	0.6 (0.2-2.4)	0.505	0.7 (0.2-2.2)	0.503	0.5 (0.1-1.8)	0.266
PHC (Yeoville and Malvern)	1	-	1	-	0.9 (0.2- 4.4)	0.941	0.7 (0.1- 3.8)	0.631	15.0 (1.7-133.6)	0.015	8.6 (0.8-87.7)	0.069	1.7 (0.4-7.0)	0.484	1.7 (0.3-8.8)	0.538
Age																
< 30	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
30-39	0.4 (0.1 - 1.8)	0.259	0.6 (0.1- 2.9)	0.496	0.7 (0.2- 2.6)	0.614	0.8 (.2- 3.1)	0.717	1.2 (0.3-4.6)	0.815	1.6 (0.3-7.6)	0.551	1.0 (0.3-3.6)	0.966	1.2 (0.3-5.0)	0.786
40-45	0.3 (0.06- 1.2)	0.079	0.5 (0.1- 2.9)	0.462	0.5 (0.1- 1.9)	0.301	0.8 (.2- 3.3)	0.717	0.5 (0.1-1.8	0.256	0.6 (0.1-3.2)	0.597	0.8 (0.2-3.0)	0.736	1.7 (0.4-7.4)	0.486
45+	0.2 (0.06- 1.1)	0.059	0.6 (0.1- 3.4)	0.595	0.3 (0.1- 1.1)	0.074	0.5 (0.1- 2.1)	0.327	0.4 (0.1-1.5)	0.160	0.7 (0.1- 3.3)	0.612	0.5 (0.1-1.9)	0.301	0.9 (0.2-4.3)	0.935
Gender																
Female	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
Male	0.7 (0.3- 1.4)	0.301	0.9 (0.4- 2.1)	0.776	0.6 (0.3- 1.3)	0.191	0.5 (0.2- 1.2)	0.139	0.5 (0.3-1.1)	0.073	0.6 (0.3-1.3)	0.244	0.7 (0.3-1.4)	0.301	0.9 (0.4- 2.1)	0.857
Relationship status																
Married	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
Single	1.5 (0.7- 3.3)	0.332	2.1 (0.8- 5.4)	0.136	1.5 (0.7- 3.4)	0.336	1.3 (0.5- 3.2)	0.598	1.1 (0.5-2.5)	0.777	0.9 (0.4-2.2)	0.799	2.0 (0.9-4.5)	0.087	2.0 (0.8-4.8)	0.143
Cohabiting	2.3 (0.9- 5.5)	0.069	3.1 (1.1- 8.9)	**0.035**	1.6 (0.7- 4.0)	0.300	1.2 (.4- 3.2)	0.751	1.0 (0.4-2.3)	0.949	0.7 (0.2-1.9)	0.470	2.0 (0.8-4.9)	0.120	2.2 (0.8-5.9)	0.134
Other	2.1 (0.5-8.7)	0.328	2.4 (0.5- 13.1)	0.301	1.8 (0.4- 7.6)	0.442	2.9 (0.5- 16.3)	0.238	0.3 (0.05-1.3)	0.105	0.3 (0.04- 1.8)	0.170	2.3 (0.5-9.7)	0.269	2.7 (0.5-14.2)	0.239
Highest education level completed																
Secondary/High School	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
Tertiary	1.6 (0.5-5.3)	0.452	2.2 (0.5- 9.3)	0.279	1.1 (0.3- 3.8)	0.827	0.9 (0.2- 3.6)	0.897	0.6 (0.2-2.0	0.422	0.8 (0.2-3.3)	0.764	1.1 (0.3- 3.7)	0.838	1.1 (0.3-4.1)	0.943
Never went to school	0.9 (0.2-3.9)	0.834	0.4 (0.1- 3.3)	0.421	0.6 (0.1-3.4)	0.602	0.8 (0.1- 5.3)	0.854	0.6 (0.1-3.0)	0.573	0.4 (0.06-2.4)	0.309	1.5 (0.3-7.0)	0.600	0.9 (0.2-5.1)	0.935
Employment status																
Employed	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
Unemployed	1.4 (0.7-2.8)	0.333	1.5 (0.7- 3.5)	0.304	0.9 (0.4-1.8)	0.705	0.8 (0.4- 1.9)	0.698	1.2 (0.6-2.4)	0.550	1.5 (0.7-3.5)	0.314	2.2 (1.1-4.3)	**0.030**	2.5 (1.1-5.7)	**0.023**
Other	1.3 (0.4- 4.0)	0.618	0.8 (0.2- 3.5)	0.798	1.6 (0.5-4.8)	0.402	2.0 (0.6- 7.1)	0.289	1.3 (0.4-4.0)	0.616	1.4 (0.4- 5.1)	0.620	1.2 (0.4-3.8)	0.699	1.3 (0.4-4.7)	0.649
Distance travelled to the facility																
5 km or less	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
6-10 km	0.8 (0.3-2.2)	0692	1.0 (0.3- 3.0)	0.959	0.7 (0.2- 1.8)	0.420	0.8 (0.3-2.3)	0.639	0.8 (0.3-2.0)	0.565	1.1 (0.4-3.2)	0.916	0.9 (0.3- 2.3)	0.771	0.9 (0.3- 2.6)	0.828
11-20 km	1.4 (0.6-3.6)	0.452	2.5 (0.8- 7.6)	0.117	0.5 (0.2-1.3)	0.145	0.6 (0.2-1.8)	0.347	0.3 (0.1-0.8)	0.017	0.5 (0.2-1.5)	0.200	0.7 (0.3-1.9)	0.513	0.8 (0.3- 2.3)	0.662
Above 20 km	0.8 (0.3- 2.2)	0.660	1.2 (0.4- 3.8)	0.790	1.0 (0.4-3.0)	0.957	1.4 (0.4- 4.7)	0.613	0.6 (0.2- 1.7)	0.344	0.9 (0.3-2.7)	0.787	0.6 (0.2-1.5)	0.262	0.6 (0.2-1.9)	0.363

Abbreviations: UOR, unadjusted odds ratios; AOR, adjusted odds ratios; p-probability value; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; HCHC, Hillbrow Community Health Centre; SRH, South Rand Hospital; PHC, primary healthcare clinic; Ref, reference; km, kilometre. All logistic regression analyses were done at 95% CI

Treatment-taking behaviour

Table 3 presents the reported treatment behaviour of the participants for the duration of receiving ART. There were more reports of treatment interruption whilst participants were on first-line treatment (*n* = 52). With respect to the reported treatment interruption whilst on second-line regimen, there was no distinct difference between the failing (*n* = 8) and suppressed (*n* = 5) groups. Both groups equally relied on themselves to remember to take their treatment ('naturally [I] remember taking my pills [VLF, woman, 31 years]; [I am] experienced on remembering my time' [VLS, man, 41 years]). Some of the reasons for interrupting treatment included stopping to take tuberculosis medication ('yes, interruption due to TB recurrence' [VLF, woman, 22 years]) and no medication availability whilst relocating ('I once interrupted my treatment due to the shortage of drugs as I relocated in South Africa and I did not have a proper transfer letter' [VLF, man, 38 years]). In the group with no reported second-line treatment interruption, more virologically suppressed participants (*n* = 21) listed using an alarm as a reminder. Several participants used the timeslots of popular local television programmes or the news (*n* = 14) as reminders to take their medication.

Table 3: History of antiretroviral treatment-taking behaviour

		First-Line Treatment			Second-Line Treatment					
		Treatment interruption	No treatment interruption	Did not report on treatment interruption	Treatment interruption		No treatment interruption		Did not report on treatment interruption	
					VLS	VLF	VLS	VLF	VLS	VLF
		52	91	6	5	8	67	56	6	7
Medication alert	Alarm	21	53	2	1	2	21	13	2	1
	TV	5	9	-	1	1	3	1	-	-
	Memory	14	14	2	1	4	30	30	3	4
	Family	7	9	1	1	-	2	4	-	-
	Did not report	5	6	1	1	1	11	8	1	2
Daily frequency	Once	16	37	1	-	2	5	1	1	1
	Twice	33	52	4	5	6	60	55	5	5
	Did not report	3	2	1	-	-	2	-	-	1
Storage	Cupboard	31	57	3	4	7	39	35	3	5
	Handbag	14	22	1	-	-	18	17	1	1
	Cooler bag/fridge	1	1	1	-	-	-	1	1	-
	Pill box	3	7	-	-	-	8	3	-	-
	Other	1	1	-	-	1	-	-	1	-
	Did not report	2	3	1	1	-	2	-	-	1

Abbreviations: VL, viral load; VLS, viral load suppression; VLF, virological failure; TV, television

Table 4 presents the bivariate and multivariate logistic regression analyses for ART-taking behaviour. There was no association between participants' treatment-taking behaviour (i.e. medication alert, daily frequencies and pill storage) and VLF. However, participants who relied on their memory as a reminder to take medication (whilst on first-line regimen) were almost three times more likely to interrupt their first-line treatment than those who relied on an alarm (AOR: 2.6, 95% CI = 1.0–6.4, p = 0.042). There was no association found between medication alert or frequency of taking medication and second-line treatment interruption. Participants who used their handbag to store their medication were the least likely to experience second-line treatment interruption (OR: 0.2, 95% CI = 0.05–1.0, p = 0.054).

Table 4: Logistic regression analysis between virological failure, regimens (first-line and second-line regimen) and treatment taking behaviour indicators in Johannesburg inner-city

Variable	Virological failure				First-line interruption				Second-line interruption			
	UOR	p	AOR	p	UOR	p	AOR	p	UOR	p	AOR	p
Medication alert												
Alarm	1	-	1	-	1	-	1	-	1	-	1	-
TV	0.8 (0.1-4.6)	0.756	0.8 (0.1-5.5)	0.837	1.3 (0.4-4.4)	0.634	1.7 (0.5-5.7)	0.429	2.8 (0.4-19.1)	0.284	2.1 (0.2-18.2)	0.497
Memory	1.7 (0.8-3.7)	0.196	1.7 (0 .8-3.8)	0.194	2.8 (1.2-6.6)	**0.023**	2.6 (1.0-6.4)	**0.042**	1.1 (0 .4-3.3)	0.818	1.1 (0.3-3.7)	0.859
Family	1.9 (0.4-8.1)	0.398	2.1 (0.5-9.8)	0.339	2.7 (0.9-7.9)	0.069	2.7 (0.9-8.4)	0.080	0.7 (0.07-6.7)	0.764	0.5 (0.08-6.5)	0.592
Did not report	1.3 (0.4-3.6)	0.677	1.2 (0.4-3.6)	0.694	2.1 (0.6-6.8)	0.236	1.6 (0.5-5.8)	0.447	1.3 (0.3-5.0)	0.745	1.5 (0.3-6.9)	0.585
Daily frequency												
Once	1	-	1	-	1	-	1	-	1	-	1	-
Twice	1.4 (0.4-5.2)	0.604	1.6 (0.4-6.4)	0.479	1.7 (0.8-3.5)	0.153	1.7 (0.8-3.7)	0.162	0.3 (0.07-1.1)	0.060	0.3 (0.08-1.5)	0.149
Did not report	0.8 (0.05-11.3)	0.835	0.8 (0.05-13.3)	0.883	4.6 (0.8-27.9)	0.095	3.7 (0.6-26.1)	0.177	Empty	-	Empty	-
Storage												
Cupboard	1	-	1		1	-	1	-	1	-	1	-
Handbag	1.0 (0.5-2.2)	1.000	1.0 (0.4- 2.2)	0.964	1.1 (0.5-2.5)	0.782	1.4 (0.6-3.1)	0.478	0.2 (0.05- 1.0)	0.054	0.2 (0.05- 1.0)	0.055
Cooler bag/fridge	0.5 (0.04-5.7)	0.577	0.5 (0.04-6.2)	0.592	3.5 (0.3-40.3)	0.312	3.8 (0.3-50.5)	0.309	1.9 (0.2-22.3)	0.602	1.9 (0.1-27.4)	0.606
Pill box	0.4 (0.09- 1.5)	0.166	0.3 (0.08-1.4)	0.131	0.9 (0.2-3.7)	0.816	1.2 (0.3-5.5)	0.809	Empty	-	Empty	-
Other	Empty	-	Empty	-	3.5 (0.3-40.3)	0.312	1.7 (0.1-22.8)	0.678	Empty	-	Empty	-
Did not report	1.0 (0.2- 5.2)	1.000	1.1 (0.2-6.3)	0.931	2.3 (0.5-11.1)	0.284	2.3 (0.4-12.2)	0.336	1.9 (0.3-11.3)	0.470	2.3 (0 .3-16.9)	0.430

Abbreviations: UOR, unadjusted odds ratios; AOR, adjusted odds ratios; p, probability value; Ref, reference. All logistic regression analyses were done at 95% CI. **Bold values indicates significant values at p<0.05**

Recommendations from participants

The study participants made 175 recommendations for improving adherence (see Table 5). Coformulation in single tablets, only needing to take one dose of medication daily (preferably at night) and education about being adherent were listed as the most effective mechanisms to improve adherence on second-line treatment. Some examples of recommendations from participants include the following:

> 'Education should be emphasised through adherence classes. Reinforce on the benefits of ART'. (VLS, female, 38 years old)
>
> 'Availing a single-dose treatment for the second-line patients would enable them to adhere to treatment. Further ongoing education would also help'. (VLF, female, 39 years old)

Other recommendations included the development of injectable ART (*n* = 9, seven women and two men) and the provision of psychosocial support (particularly related to poverty and ensuring food supply):

> 'Should consider addressing the psychosocial needs of patients on second-line as they have to adhere to treatment but sometimes, they do not have enough food to eat'. (VLF, female, 45 years old)

Single recommendations to improve adherence included treatment reminders (*n* = 1), additional counselling (*n* = 1) and minimising the number of times second-line regimen is taken per day (*n* = 1). One patient felt that healthcare workers trusting that their patients took their medication as prescribed would promote treatment adherence. Lastly, 12 participants did not have any recommendations (mainly because of not experiencing any pill-taking challenges), as shown in the following statement:

> 'The current regimen is fine with me, therefore, I will suggest no change'. (VLS, male, 41 years old)

Table 5: Participants' perspectives on how adherence can be improved amongst patients on second-line ART

Recommendation	Number of people citing the recommendation
Coformulation in single tablets	55
One dose	46
Education	24
No recommendations	12
Injection	9
Psychosocial support	9
Smaller pills	7
No side effects	4
Clinic operating times	2
Counselling	1
Decreased frequency of treatment ingestion	1
Follow-up	1
Liquid	1
More research needed	1
SMS [3] reminders	1
Trust patients	1
TOTAL	175

Abbreviation: SMS, Short Message Service

[3] Text message

DISCUSSION

This study sought to describe and understand treatment adherence and possible treatment support interventions from patients receiving second-line ART.

It has been reported that relationship dynamics influence ART adherence and VLS in that being married or having a committed and supportive partner tended to foster an environment for better clinical outcomes in HIV-positive people [17,18]. Studies from South Africa and the United Kingdom found that HIV-positive married individuals had better clinical outcomes compared to any other relationship status [19,20]. Similarly, our study found that single and unmarried people living with their partners were more likely to be virally unsuppressed.

Not statistically significant but important for consideration in adherence strengthening, our study showed that being younger was a predictor of VLF, which was congruent with previous studies [21,22,23]. We noted VLS in those participants who resided further away from the health facilities. This is not in agreement with findings of studies conducted in Uganda, Ghana and Burkina Faso [24-26], which reported that individuals who resided closer to a health facility were more likely to seek healthcare.

Late disclosure may hinder adherence or treatment support and subsequently yield poor clinical outcomes [27]. Whilst the majority of participants (63%) disclosed their HIV status 1 week after diagnoses, about 28% took longer than 4 weeks to disclose. Early disclosure, particularly to a family member or partner, has been strongly associated with improved adherence [8,28,29]. Disclosure to a family member or partner has been linked with adequate psychosocial support which in turn facilitates adherence to treatment [8,29-32]. However, the findings of our study suggest that disclosure and dependence on a treatment supporter are likely not to produce desired adherence levels (and did not feature in the list of participant recommendations), indicating that disclosure and treatment support should be assessed in combination with other adherence strategies instead of as a single consideration or mechanism [33].

Unsurprisingly, the more toxic the second-line multi-pill, and regimens requiring medication to be taken multiple times a day, were seen as significantly harder to take than a single tablet daily well-tolerated first-line regimen. These views were consistent with reports from other studies that attributed similar challenges to taking second-line regimen [34-36]. Participants who did not interrupt ART mainly reported using an alarm as a reminder for taking their medication. This finding suggests the need to explore external reminder mechanisms for improving adherence in this setting, considering that about 15% of VLF participants reported not using any external reminders. Various studies have also found a trend towards better adherence amongst patients who used external reminders [37-39]. In addition, our study showed that participants who used their handbags to store their medication were more likely to adhere to treatment. This finding is in line with other studies that have reported having a handbag to have pills all the time as the preferred ART storage by patients [40-42].

Side effects are an important predictor of poor adherence, and cumulative toxicity associated with ART, especially in second-line regimens [43-45]. We found that participants with VLF were more likely to have treatment-related side effects. Furthermore, those participants with side effects were more likely to be unemployed. Although this was not explored further in our study, various studies have reported that employed patients can manage their health and side effects better than their unemployed counterparts [46-48].

Participants had ideas regarding drug formulation that may improve adherence. These included a fixed-dose combination, a dosage taken once a day and reducing the pill size. Furthermore, the participants suggested that education on the benefits of taking ART could improve adherence, whilst a few participants also suggested the implementation of injectable ART. Various studies have recommended similar strategies [49-51], with the effectiveness of some of these strategies being previously reported for
first-line regimens [51,52].

Study limitations and strengths

This study had several limitations. Firstly, the study relied on participants' self-reports, prompting a likelihood that socially desirable answers may have been provided. However, to control for this, information such as viral load, side effects and comorbidity was verified by checking participants' medical records as part of data quality checks for the study. Secondly, the clinical measure for adherence considered viral load only. Finally, the sample might be small for the results to be generalised to all patients receiving second-line ART. However, the direction and size of effect were generally consistent, suggesting that the study findings may be robust despite these limitations.

CONCLUSION

Participants on a second-line antiretroviral regimen had firm recommendations regarding improving adherence, largely focused on administration, reduced dosing and pill burden. The study results suggest the importance of improving patients' knowledge about treatment and adherence and motivation to continue ART use despite the persistence of side effects. Drug manufacturers and health programmers must consider such recommendations as they modify and implement new ART regimens and programmes. Lastly, treatment support interventions recommended in this study need to be tested in practice to determine their efficacy for large-scale implementation.

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CHAPTER 7

Intervention strategies to improve adherence to treatment for selected chronic conditions in sub-Saharan Africa: A systematic review

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ABSTRACT

Introduction: Evidence-based intervention strategies to improve adherence among individual living with chronic conditions are critical in ensuring better outcomes. In this systematic review we assessed the impact of interventions that aimed to promote adherence to treatment for chronic conditions.

Methods: We systematically searched PubMed, Web of Science, Scopus, Google Scholar, and CINAHL databases to identify relevant publications and used the GRADE, QUIPS and EPHPP assessment tools to assess the quality and risk of bias of each study. We extracted data from eligible studies for study characteristics and description of interventions for the study populations of interest.

Results: Of the 25 473 total studies/records screened, 2645 were eligible for abstract screening and of those, 466 were eligible for full text screening. A total of 77 studies were subsequently included, describing a total of 49 364 patients. Of the total included studies, 54 (70.1%) were related to antiretroviral therapy (ART) for HIV, 6 (7.8%) were anti-hypertensive medication related, 12 (15.6%) were anti-diabetic medication related and 5 (6.5%) focused on medication for more than one condition. A total of 46/77 (59.7%) reported improved adherence based on the described study outcomes while 16/77 (20.8%) reported no significant difference between studied groups. The 77 publications described 91 unique interventions (some studies described more than one intervention). Among these intervention strategies, 12 (13.2%) were multifaceted (4/12, (33.3%) multi-component health services- and community-based programs, 5/12 (41.7%) included individual plus group counselling, 3/12 (25.0%) included SMS or alarm reminders plus individual counselling).

Discussion: The interventions described in this review ranged from adherence counselling to more complex interventions such as mhealth interventions which took into consideration patients' abilities to use digital technology. Combined interventions comprise of different components may be more effective than using a single component in isolation. However, complexity involved in designing, implementation and replicating combined interventions, often complicates the practicalities of such interventions.

Conclusion: There is substantial evidence that community-and home-based interventions, digital health interventions and adherence counselling interventions can improve adherence to medication for chronic conditions. Future research should answer if existing interventions can be used to develop less complicated multifaceted adherence intervention strategies.

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INTRODUCTION

Patients on treatment for chronic conditions face multiple barriers to adherence, and no single intervention is deemed sufficient to ensure that high levels of adherence to treatment are maintained [1]. There remains a need to strengthen and tailor different intervention strategies to different barriers to adherence for chronic conditions [1].

In the efforts to address adherence to treatment for the chronic conditions; behavioural and psychological factors, education, integrated care and patient self-management interventions have been explored [2,3]. This includes behavioural rehabilitation provided by health providers to patients, integration of pyscho-social support within health programmes, and patient's knowledge about the medication and their overall satisfaction with the treatment [4–6]. Other studies have recommended telephonic counselling and text messaging or reminders (mobile health/mhealth), packaging/medication boxes, home visits, drug level monitoring, consistent clinical monitoring of patients [4,6,7]. Studies focusing on adherence to Antiretroviral Therapy (ART) for Human Immunodeficiency Virus (HIV) have further emphasized the importance of compliance with standard treatment guidelines (monitoring and reporting of health information (data) to promote appropriate medicine use [8–10]. Interventions that use mobile technology (mhealth) have the potential of facilitating self-management, education, and support, unfortunately mhealth applications have been limited in sub-Saharan Africa (SSA), and they have had mixed effects on controlling non-communicable diseases (NCDs) [11,12].

Although numerous reviews have evaluated adherence interventions [12–16], few have undertaken a comparative analysis of adherence to medication for various conditions, notably HIV, Hypertension (HPT), and Diabetes Mellitus (DM). While HIV remains the leading cause of death more especially in the young and middle-aged adults in SSA, the burden of NCDs, particularly HPT and DM, has increased rapidly in recent years [17–19] and understanding adherence to related medication is a priority issue. This review assesses treatment adherence interventions for established and emerging chronic conditions in SSA, which provides valuable comparisons and context to adherence interventions strategies for the chronic conditions in SSA.

METHODS

This systematic review has been designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[20] (Supplementary material 1), following the registered protocol on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019127564) [21]. The study used Population (P), Interventions (I), Comparisons (C) and Outcomes (O) (PICO) criteria as the search strategy tool.

Eligibility criteria

All studies assessing the impact of adherence interventions for ART, anti-hypertensive medication, and anti-diabetic medication in SSA that were conducted or published between 01 January 2000 and 30 November 2022 were considered for inclusion. Studies were excluded if the study setting was not SSA, if papers were written in any other language than English, if the health condition for which adherence to medication was assessed was not HIV, HPT or DM, and if the study was published before the year 2000 (Table 1).

Table 1: Methodological aspect of the systematic review

Criteria for study inclusion	Components details
Population (P)	Patients/participants with selected chronic conditions (HIV, HPT, DM) in SSA
Intervention (I)	All interventions listed/described as medication adherence interventions or strategies for the conditions of HIV, HPT, DM
Comparisons (C)	Standard of care and other adherence interventions reported in the relevant study
Outcome (O)	There is no preferred measurement for reporting. For this review, we included studies that reported any quantitative measure of medication adherence including self-reported adherence using a defined threshold, pill count using a defined threshold, change in CD4+ lymphocyte count and HIV-1 RNA (viral load), mean change in systolic blood pressure (SBP) and/or systolic blood pressure (DBP) measured at certain intervals, retention in care and LTFU, weight, a reduction in HbA1C level, improved specific self-efficacy, mean change in weight, mean waist circumference, mean HbA1c, and medication adherence using Morisky Medication Adherence Scale (MMAS-8). Effects on adherence behaviour and the changes in health outcomes.
Setting	All studies from SSA only were considered for the review.
Language	English
Publication date and study duration	Year 2000 to 2022
Publication status	All the documented studies were considered and included for review. This includes peer reviewed (i.e., papers, manuscripts, and abstracts) and dissertations or thesis.

Data Collection

We conducted a systematic data search using several electronic databases, including PubMed Web of Science, CINAHL, Scopus and Google Scholar, between 01 August 2021 and 15 December 2022. These dates included repeat searches in case of article publications occurring after the initial search. We also reviewed citations and bibliographies of other related reviews to identify additional relevant material.

The search terms were adjusted to suit the database being searched. An inventory with the database searched, the corresponding search criteria used, the date when the searches were conducted, and the results were all maintained (supplementary material 5_search term strategy). Two other reviewers (Lisa Noordman and Marit Wiltink) ran the searches separately for comparison. The comparison entailed number of articles showing as a result of each search (search hits). Small differences were observed and attributed to different dates in which databases were accessed and/or searched by the reviewers. In this case, results from each reviewer were merged and deduplicated.

Three reviewers (S.B.G, Lisa Noordman and Marit Wiltink) independently conducted title and abstract screening, The screening results were compared for each reviewer to identify any discrepancies. Discrepancies in the screening results were discussed between the three reviewers. In cases where an agreement on inclusion could not be reached, a fourth reviewer (S.T.L.E) made the final decision.

From the database search engines, data was imported into Rayyan electronic tool, a free web-tool designed to help synthesize data for systematic reviews, scoping reviews and literature reviews [22].

Study Selection

The reviewers performed title and abstract screening using a predefined list of inclusion and exclusion criteria (Table 1 and figure 1). In case the article was not specific or clear enough, especially in terms of intervention type and outcome measures, screening was discussed by all the reviewers and S.T.L-E made the final decision. Multiple studies of the same cohort were included if different outcomes were studied.

Data Extraction

Data was extracted using a standardized form. The following details were extracted: study title, first author, publication year, type, study duration, country, population, study geographical setting, study design, sample size, intervention description, details on age, sex, condition (HIV, HPT, DM), outcome measures, and main results.

Quality Assessment

For all studies in the systematic review, assessments of quality and risk of bias were performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [23,24], Quality in Prognostic Studies (QUIPS) [25] and Effective Public Health Practice Project (EPHPP) [26] tools applied to our research question (Supplementary material 2, 3, 4). These different risk of bias/quality assessment instruments/tools were used because of their suitability to different study designs. The risk of bias was assessed as low risk, moderate risk, or high risk for each of the following domains: study design, participant selection, study sample size, descriptions of outcomes, and description of interventions.

Data Analysis

For each study included in the review, the following characteristics were recorded: authors, year of publication, country where the study was conducted, study duration, study design, study site/setting, study population/sample, sample size, sex of participants, age of participants, health condition studied, intervention assessed, outcomes analyzed and main findings. Adherence interventions were described according to type of intervention and implementation setting.

RESULTS

Description of included studies

A total of 25 473 records were screened and after removal of duplicates, a total of 23 898 records remained and their titles and abstracts were screened for inclusion. Of the 23 898 records, 2645 were further screened for inclusion by abstract. The full text screening of potentially eligible articles was subsequently done in 466 records. The reasons for exclusion of papers are noted in Figure 1. In total, 77 articles [27,28,37–46,29,47–56,30,57–66,31,67–76,32,77–86,33,87–96,34,97–103,35,36] were found to be eligible and data was then extracted (Table 2).

Of the 77 articles, 70/77 (90.9%) were peer-reviewed journal articles, 7/77 (9.1%) were dissertations, and 1/77 (1.3%) paper abstract. Fifty-four papers reported studies of interventions to promote adherence to ART, six were anti-hypertensive medication related, 12 were anti-diabetic medication related and five focused on more than medication for more than one condition. Almost half of included studies (37/77, 48.1%) were conducted in Southern African region, with a total of 35 319/49 364 participants (71.5%) and East Africa (28/77, 36.4%) with a total of 9 972/49 364 participants (20.2%) (Table 2). The remaining 12/77 (15.6%) studies with 4 073/49 364 (8.3%) participants were conducted in other parts of sub-Saharan African region (including West Africa and Central Africa). The studies included reported findings on a total of 49 364 participants. Mean sample size was 667 participants (range: 10–10 136). The median age of participant samples was between 30 and 40 years and about two-thirds of the study participants were women.

Of the included papers, 31/77 (40.3%) reported findings of evaluation studies, including randomized controlled trials (28/30, 90.3%) and quasi-experimental studies (3/30, 9.7%), 19/77 (24.7%) reported findings of correlational studies, notably cross-sectional surveys (11/18, 61.1%), and cohort studies (7/18, 38.9%), 17/77 (22.1%), reported findings of explorative research (qualitative research) and 4/77 (5.2%) were mixed method studies. The remaining 8/77 (10.4%) papers included various study designs such as, non-described descriptive studies. Data was collected between 2003 and 2022 and the year of study publications ranged from 2006 to 2022.

A total of 46/77 (59.7%) reported improved adherence based on the described study outcomes, 15/77 (19.5%) did not have clear results or defined outcomes, and 16/77 (20.8%) reported no significant difference between studied groups. Of the studies reporting improved medication adherence, 22/46 (47.8%) were community-and homed-based interventions, 11/46 (23.9%) were mhealth interventions, 7/46 (15.2%) were adherence counselling interventions 4/46 (8.7%) were educational interventions, 1/46 (2.2%) ART optimization intervention and 1/46 (2.2%) was health service intervention (Table 2 and 3).

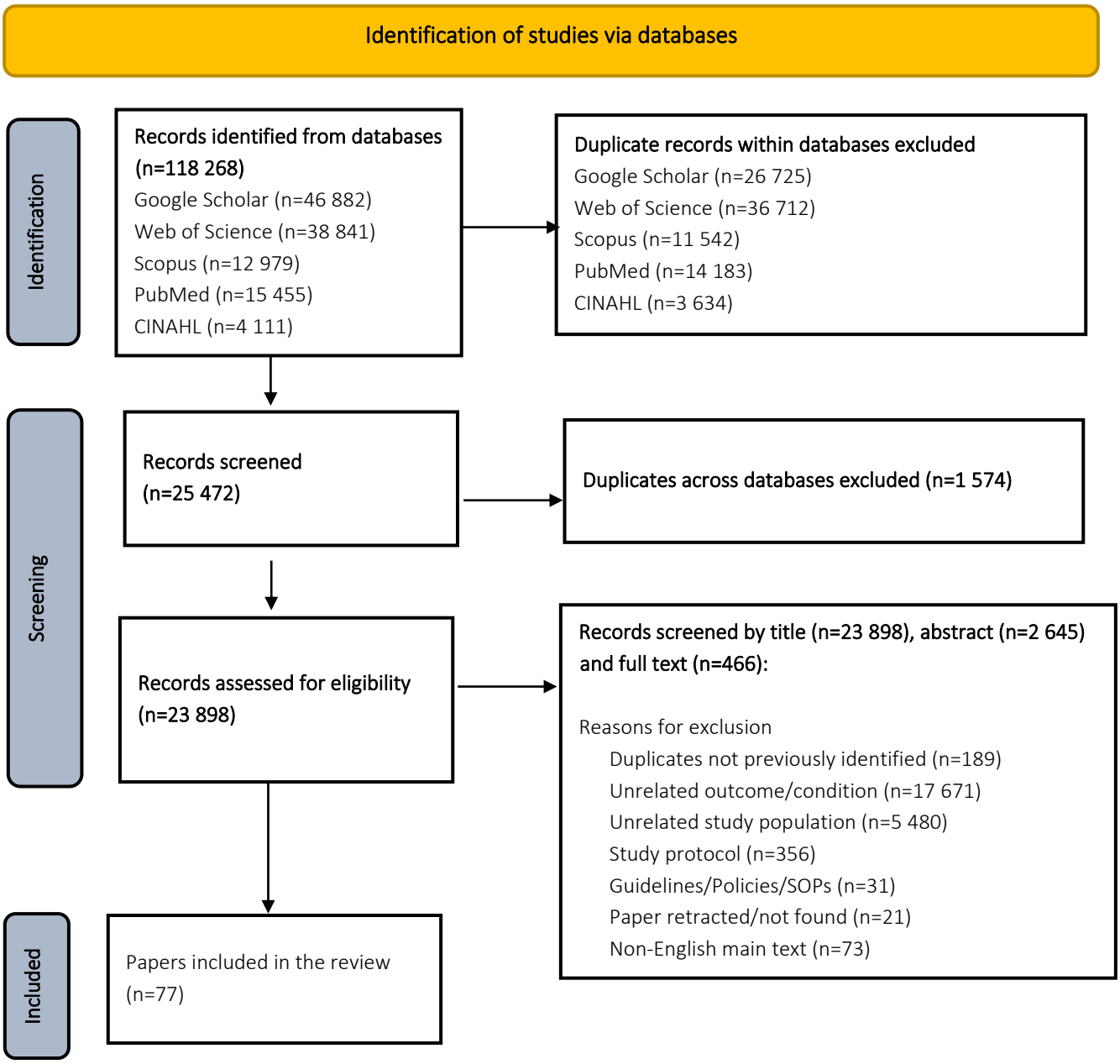

Figure 1: Flow Chart- Identification of studies via databases

[Insert Table 2 here]

The 77 publications described 91 unique interventions (some studies described more than one intervention). Among studies, majority were ART related interventions (68/91, 74.7%), followed by anti-diabetic (14/91, 15.4%) while anti-hypertensive related interventions were the least (9/91, 9.9%).

Of the 37 community-and home-based interventions, peer treatment supporters (14/37, 37.8%), nutrition support (7/37, 18.9%), and community-based social network support (10/37, 27.4%) were the most described community-and home-based interventions. Of the total

mhealth-based interventions, SMS reminders at a regular interval (10/18, 55.6%) was the most described mhealth-based intervention. (Table 3).

Other interventions included adherence counselling (27/91, 29.7%), health service interventions (2/91, 2.2%) (which included decentralization of services and health systems strengthening,) incentive intervention (voucher) (1/91, 1.1%), and drug optimization (transition in medication) (2/91, 2.2%).

Of the 91 unique intervention strategies, 12 (13.2%) were multifaceted (4/12, (33.3%) multi-component health services- and community-based programs, 5/12, (41.7%) included individual plus group counselling, 3/12 (25.0%) included SMS or alarm reminders plus individual counselling) (Table 3).

Table 3: Description of adherence intervention types

Intervention Type	Definition	ART	Anti-hypertensive medication	Anti-diabetic medication
Community-and Home-based interventions				
Community Based-Adherence Support (CBAS) with home visits	Provision of adherence support through home visits by a community health worker or peer volunteer. Home visitors are involved in a variety of activities such as food ration provision basic clinical assessments and patient referrals, ART delivery, providing DOT and pill counts.	2	0	0
Multi-component health services-and community-based program	Interventions involving a facility-designated health worker who connects patients to facility-level services. Responsibilities of the worker have include home visits, patient monitoring and tracing, and counselling.	4	0	0
Peer treatment supporters	Involving other persons within a patient's social circle in assisting that patient with their treatment. Examples of responsibilities of the treatment supporter include providing DOT service, social support, bonding, bridging or linking social networks, clinical site mediation and providing regular follow-up reminders for the next appointment attendance.	9	2	3
Community-based social network support	Support at the community level designed to be delivered to a group. Includes interventions involving a patient's extended social network in the patient's treatment.	6	2	2
Nutrition support	Providing supplementary nutritional support either at the individual or household level. Can come in the form of food rations or nutrition education.	7	0	0
Total		**28**	**4**	**5**
Digital health/mhealth/ehealth Interventions				
SMS reminders sent at regular intervals	Regular delivery of SMS messages aimed at directly or indirectly reminding patients to adhere to their medication.	8	1	1

SMS reminders triggered by adherence monitors	SMS messages were sent if an electronic adherence monitoring device were not opened within 30 minutes of the schedule dose time.	1	0	0
IVR or phone calls for reminders	Interactive voice response or regular phone calls delivering messages on medication adherence and other HIV/ART related topics, as well as appointment reminders. Some also sent non-interactive, SMS picture messages to remind patients of dosage adherence.	1	0	0
Smartphone application	Medication reminders and adherence tracking, refill and appointment reminders, leaderboard and adherence points, social support through discussion forms, peer-to peer support, and community-based resources list	1	0	0
Ehealth: Adherence monitor deviceI	A device enabling healthcare professionals or researchers to interpret activities of the patient/participant in the context of adherence and inform better decision making and as an intervention and tool for the patient to aid self-management and improve adherence.	2	0	0
Total		**13**	**1**	**1**
Adherence Counseling				
Individual counselling	Adherence educational and/or counselling interventions delivered in a one-on-one setting. Sessions are often led by trained health professionals or lay counsellors (including direct social support).	6	2	5
Group counselling	Adherence educational and/or counselling interventions delivered in a group setting. Includes social support groups. Sessions are often led by trained professionals or lay counsellors and delivered through a set curriculum or informed by a psychosocial theory/practice.	5	1	0
Individual plus group counselling	Interventions with both individual and group counselling components (including educational and/or counselling delivered in a one-on-one or group setting)	5	0	0

Adherence counselling: SMS or alarm reminders plus individual counselling	Individual adherence counselling combined with regular reminders. Reminders could come in the form of either an alarm device programmed around dosage times or regular SMS messages, sent at times independent of the dosage schedule.	3	0	0
Total		**19**	**3**	**5**
Health service interventions				
Decentralization : Decentralized Medication Delivery(DMD)	Decentralization comprises clinically stable ART patients who meet at facilities or community locations in groups of up to 30 every 2 to 3 months to receive group counselling, have a brief symptom screen, and receive prepacked medications. DMD comprises prepacking and distribution of medications to pick-up-points, which are at locations other than the clinic pharmacy. Patients only need to come to the clinic on a 6-monthly basis for a clinical exam and rescripting	1	0	0
Health system strengthening program	A well-functioning health system working in harmony is built on having trained and motivated health workers, a well-maintained infrastructure, and a reliable supply of medicines and technologies, backed by adequate funding, strong health plans and evidence-based policies.	1	0	0
Total		**2**	**0**	**0**
Incentive intervention (behaviour change mechanism)				
Voucher	Vouchers are cash or gifts with a definitive value provided to study participants. The voucher incentive interventions are offered and designed by the researchers or investigators to reward participants/patients for achieving a certain goal and encourage team members to exceed their goals.	1	0	0
Total		1	0	0
Drug optimization				

Transition in medication	The adoption of better drug regimens to improve treatment adherence, viral suppression and quality of life of people living with the specified condition. These benefits could reduce pressures on health systems as lower rates of viral failure on new treatments could reduce the risk of HIVDR and HIV transmission. In addition, transition to new lower-cost ARV drugs could provide significant savings for national health budgets worldwide.	2	0	0
Total		**2**	**0**	**0**
Educational intervention				
Active visualization device	A device that delivers or provides health information that could be particularly useful in educating patients about the specific condition or related treatment.	1	0	0
Health education/knowledge	Any combination of learning experiences designed to help individuals and communities improve their health, by increasing their knowledge or influencing their attitudes.	1	1	2
Health literacy	The achievement of a level of knowledge, personal skills and confidence to take action to improve personal and community health by changing personal lifestyles and living conditions.	0	0	1
Total		**2**	**1**	**3**
Other				
Intervention counting pills	monthly clinic-based pill counts,	1	0	0
Total		**1**	**0**	**0**
Overall total		**68**	**9**	**14**

Risk of Bias

Risk of bias was measured using GRADE, QUIPS and EPHPP tools (supplementary material), based on the study design, participant selection, study sample size, descriptions of outcomes, and description of interventions. Of the 31 papers (including randomized control trials and quasi-experimental), 25/31 (80.6%) scored a low risk of bias, 4/31 (12.9%) a moderate risk of bias and 2/31 (6.5%) reported a high risk of bias. Out of 19 correlational papers (cohort and

cross-sectional studies), 14/19 (73.7%) scored a low risk of bias and 5/19 (26.3%) scored a moderate risk of bias. From the 17 explorative studies (qualitative studies), only 2/17 (11.8%) scored low risk of bias, 11/17 (64.7%) scored a moderate risk of bias and 4/17 (23.5%) scored high risk of bias. From the other study designs (mixed and non-described descriptive methods) 5/10 (50.0%) scored low risk of bias, 3/10 (30.0%) scored a moderate risk of bias and 2/10 (20.0%) scored a high risk of bias. Overall, 46/77 (59.7%) scored a low risk of bias, 23/77 (29.9%) a moderate risk of bias and 8/77 (10.8%) a high risk of bias. Most papers scored well on participant selection, study design, outcome measurement, intervention measurement, data collection methods and data analyses.

DISCUSSION

There has been a significant increase in the number of studies implementing and evaluating interventions aimed at promoting adherence to chronic conditions. This systematic review combines the available evidence from a large number of studies to identify a range of adherence interventions aimed at promoting adherence to ART among HIV-infected patients, anti-hypertensive medication, and anti-diabetic medication. Majority of adherence interventions described in this review were ART related. This is consistent with health programmes in most sub-Saharan African countries that have placed more focus in HIV programmes as compared to HPT and DM related programmes, but different to most high-income countries whose focus has been balanced across the three chronic conditions [8,104–106].

Individual-related characteristics described in the reviewed studies demonstrated that almost two-thirds were females, and of middle age (30-40 years). The individual specific characteristics identified may represent the demographic profile of patients in chronic treatment programmes, particularly those receiving HIV care in the SSA [107,108]. The community-based adherence interventions highlighted an important link between primary healthcare facilities or services and the communities, demonstrated an integration of treatment and patient care, and decentralization of chronic care to the communities [109,110]. Community-and home-based adherence interventions such as peer treatment support meets the rising need associated with the overall chronic care, where due to the real shortage of healthcare workers and the growing caseload of people needing care, professional workers roles are increasingly limited to medical and nursing tasks in health facilities [111]. This review provides evidence of the efficacy of community-and home-based adherence support strategies, but more focus should be on their acceptability and cost-effectiveness.

Mobile health is increasingly being explored for health promotion [112] and was also used in adherence promoting interventions identified in this review, in order to deliver educational, and behavioural components, either singly or in combination. Majority of mhealth related medication adherence interventions described in this review reported improved adherence using specified outcome measurements. Most mobile health interventions were used to

educate, remind, or provide advice to patients. These technologies enabled the collection and transfer of patient specific data/information across to different professionals, who could then deliver the tailored feedback and reminders to the patients. The increasing advancement in technology and related benefits received by patients from health care providers without presenting at a health facility is an appealing prospect. Furthermore, mhealth interventions could have a greater reach, better adoption and implementation; thus having a greater positive heath impact [112,113]. However, more research is needed to establish the sustainability of such interventions and to evaluate how mhealth interventions can be useful in the short and long term in promoting adherence to medications.

The interventions described in this review were primarily directed at patients and ranged from adherence counselling including both individual and group counselling to more complex interventions such as mhealth interventions which took into consideration patients' abilities to use digital technology and preferences in addition to educating and aiding them to adhere to medication. Some of the interventions employed a combination of interventions, for an example, adherence intervention consisting of a combination of educational, behavioural or affective strategy. Behavioural and affective strategies, which are increasingly being used in adherence support interventions, ranged from adherence aids (such as medication administration aids), to motivational interviewing [114,115].

Individual and group counselling adherence interventions could be regarded as being more patient centred, however their impact depend on the extent to which patients' or individuals' psychosocial needs are taken into consideration. This includes attitudes towards the health condition, cultural barriers, social concerns (such as perceived stigma), and cognitive abilities. These needs have been recognised in recent years as important predictors of optimal adherence to treatment and should be considered in any development of adherence interventions for chronic conditions [116].

The role of health care service-related interventions on medication adherence has been emphasized, particularly in cases of chronic diseases [117], though their impact are difficult to measure and have often been found to lack consistency [117,118]. More adherence interventions have also addressed health care services related factors impacting adherence, as was seen in this review. These include patient-related, condition-related, and medication-related factors. For an example, this review reported that adoption and using better ART drugs treatment, improved adherence to medication. In addition, greater emphasis on task-shifting and decentralization of services improved medication adherence and is therefore, worthy of further investigation.

This review also reported improved medication adherence and retention in care for participants who received cash vouchers during the study period. The early effects on adherence and retention were sustained in the cash groups after the intervention was

complete. Although this intervention improved adherence, the effect of such interventions should be considered along with other tested interventions as part of a comprehensive package of support during the treatment journey. A larger-scale impact evaluation to determine the effectiveness of cash support on cost-effectiveness, and issues related to sustainability also needs consideration.

Overall, human behaviour is a complex fact. It is therefore more likely that any intervention designed to influence human behaviour, such as modifying medication adherence in patients with chronic conditions, would be more successful if multiple factors that aid the change in human behaviour are addressed. Combined interventions comprise of different components, which may act both independently and inter-dependently, to address the changes needed, and may be more effective than using a single component in isolation [119]. However, complexity involved in designing, implementation and replicating combined interventions, often complicates the practicalities of such interventions [119]. Therefore, interventions involving a single component may be preferred as they are easier to design, implement and replicate, and often times are successful in influencing a behaviour change [119].

Limitations of the reviewed studies

The quality of the studies included in this review varied; Our assessment of a study's quality was often limited due to a failure to report critical information such as participant inclusion criteria, or to adequately describe outcome measures. A lack of methodologically rigorous, makes it difficult to assess the quality of the study, risk of bias and draw conclusions. More rigorous research in this field is critical, as is replication of studies with positive findings in other settings. Furthermore, some of the studies described in this review were multifaceted, with some delivering multiple intervention components and others providing adherence support as a part of a broader package of services; this makes it impossible to discern the relative effect of each intervention component or identify which aspects are most impactful on adherence. Another limitation of these studies, and of adherence research in general, remains with the challenge of accurately measuring medication adherence and in the variety of methodologies utilized. Beyond issues of validity and precision of each measure used, it is difficult to compare the effectiveness of studies reporting different measures or different definitions of optimum adherence.

CONCLUSION

Our study found substantial evidence on interventions to improve adherence among adults living with chronic conditions in SSA. There is larger evidence that community-and home-based, mhealth and adherence counselling interventions can improve adherence to chronic conditions. These tested and evaluated adherences enhancing interventions should increasingly be considered for routine implementation in health programmes. However, rigorous on-going evaluation of the impact and performance of these interventions will be necessary. Multifaceted adherence interventions strategies that include reliable adherence

measures such as drug exposure testing and socio-economic support components such as cash vouchers provided to patients, may be more effective than using a single component intervention strategy. Therefore, evidence gaps on adherence enhancing interventions need to be closed, including on cost-effectiveness and long-term effectiveness. Future research should seek to answer if existing intervention strategies can be successfully adapted for all chronic conditions assessed in this review. Our findings support testing more interventions and the need to develop a gold standard (or uniform measures) for adherence outcome ascertainment.

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Table 2: Characteristics of included studies

Study title	First author, publication year	Type	Study duration	Country	Population	Setting	Study design	Sample size	Intervention description	Details on age (median, mean, range)	Sex	Condition (HIV, HTN, DM)	Outcome measures	Main results
A peer adherence support intervention to improve the antiretroviral treatment outcomes of HIV patients in South Africa: the moderating role of family dynamics	Wouters et al., 2014	Journal article	2007-2008	Free State Province, South Africa	HIV positive patients who are on ART	Public-sector ART programme of the Free State Province of South Africa	Cross-sectional secondary statistical analysis of post-trial data	340	Peer adherence support intervention	37.0 (SD±9.1)	Female (77.4%)	HIV	Treatment outcomes were assessed using the patients' CD4 cell counts, recorded closest to the date of the interview and extracted from the patients' files and electronic records	No significant overall differences in CD4 cell count between the intervention group accessing additional peer adherence support and the control group receiving standard care. When controlling for the potential moderating role of family dynamics, the outcomes showed a significant interaction effect between the adherence intervention and the level of family functioning with regard to treatment outcomes. Multi-group analysis demonstrates that peer adherence support has a positive effect on immunological restoration in well-functioning families, while having a negative effect in dysfunctional families
A randomized control trial of a peer adherence and nutritional support program for public sector antiretroviral patients	Booysen et al., 2016	Policy Research Working paper	Not specified	Free State Province, South Africa	HIV positive patients who are on ART	Public health care setting in South Africa	Prospective cohort study and experimental study	653	Peer adherence and nutritional support	37 (IQR 31-43)	Female (76.8%)	HIV	The impact of these peer adherence and nutritional support interventions on self-reported adherence, timeliness of clinic and hospital visits, and immunologic response to antiretroviral treatment	Peer adherence and nutritional support improved the timeliness of adults´ clinic and hospital visits for routine follow-up while on antiretroviral treatment. Peer adherence support impacted positively on immunologic response to antiretroviral treatment
A randomized controlled trial of real-time electronic adherence monitoring with text message	Orrell et al., 2015	Journal article	2012-2014	Gugulethu, Cape Town	HIV positive patients on first-line ART	Large public sector urban ART outpatient clinic	Randomized controlled trial in ART-naive individuals	230	Simple text message that would remind patients to take their tablets, but not disclose their HIV status to others at	34.5 (SD±9.1)	Female (65.2%)	HIV	The primary outcome was adherence execution as measured by the electronic adherence monitoring device (EAMD). Adherence execution was calculated by the number of days the	Median adherence was 82.1% (interquartile range, 56.6%–94.6%) in the intervention arm, compared with 80.4% (interquartile range, 52.8%–93.8%) for SoC [adjusted odds ratio for adherence 1.08; 95% confidence interval (CI): 0.77 to 1.52]. Suppressed HIV RNA (<40 copies/mL) occurred in 80 (69.6%)

dosing reminders in people starting first-line antiretroviral therapy									home or in the community				container was opened over the number of days in the period in care (for those who completed the study, transferred out or who died); and for the period from randomization to calculated week 48 for those LTFU.	of control and 75 (65.2%) of intervention (adjusted odds ratio for virological failure in intervention arm 0.77; 95% CI: 0.42 to 1.40). In the intervention arm, the count of TIs of >72 hours was reduced (adjusted incident rate ratio, 0.84; 95% CI: 0.75 to 0.94)
Adherence clubs and decentralized medication delivery to support patient retention and sustained viral suppression in care: Results from a cluster-randomized evaluation of differentiated ART delivery models in South Africa	Fox et al., 2019	Journal article	2015-2016	Gauteng, North West, Limpopo, and KwaZulu Natal-South Africa	HIV patients who are on ART	The study was conducted in 24 health facilities (12 intervention, 12 control sites) in Gauteng, KwaZulu Natal, Limpopo, and North West provinces	Unblinded cluster-randomized evaluation design	569	Adherence Clubs (ACs) and Decentralized Medication Delivery (DMD): ACs comprise clinically stable ART patients who meet at facilities or community locations in groups of up to 30 every 2 to 3 months to receive group counseling, have a brief symptom screen, and receive prepacked medications. DMD comprises prepacking and distribution of medications to PuPs, which are at locations other than the clinic pharmacy. Patients only need to come to the clinic on	61% were aged 30–49 years	AC: 71% of patients were female. DMD: 70% female	HIV	Outcomes were retention and sustained viral suppression (<400 copies/mL) 12 months after AC or DMD enrollment (or comparable time for controls)	AC patients had higher 1-year retention (89.5% versus 81.6%, aRD: 8.3%; 95% CI: 1.1% to 15.6%) and comparable sustained 1-year viral suppression ((89.5% versus 81.6%, aRD: 8.3%; 95% CI: 1.1% to 15.6%) and comparable sustained 1-year viral suppression (<400 copies/mL any time <= 18 months) (80.0% versus 79.6%, aRD: 3.8%; 95% CI: −6.9% to 14.4%). Retention associations were apparently stronger for men than women (men RD: 13.1%, 95% CI: 0.3% to 23.5%; women RD: 6.0%, 95% CI: −0.9% to 12.9%). For DMD, 232 intervention and 346 control patients were enrolled; 71% of patients were female, 65% were aged 30–49 years, and median CD4 count at ART initiation was 270 cells/μL. DMD patients had apparently lower retention (81.5% versus 87.2%, aRD:−5.9%; 95% CI: −12.5% to 0.8%) and comparable viral suppression versus standard of care (77.2% versus 74.3%, aRD: −1.0%; 95% CI: −12.2% to 10.1%), though in both cases, our findings were imprecise

								a 6-monthly basis for a clinical exam and rescripting					
Adherence counseling and reminder text messages improve uptake of antiretroviral therapy in a tertiary hospital in Nigeria	Maduka et al., 2013	Journal article	2011	Nigeria	ART non adherent patients	Tertiary health care institution in Nigeria	Randomized control trial among non-adherents	104	The intervention group received monthly adherence counseling and twice weekly short message reminders for four months, while the control group received only standard care.	Control: 35.3 (SD± 9.04) and intervention: 36.6 (SD± 11.77)	Females (56.7%)	HIV	Self-reported adherence: This was calculated based on client self-report of number of pills missed in the past seven days. The results for the intervention and control groups were compared to ascertain any changes in CD4 levels pre- and post-intervention and the magnitude of such changes if present.	Adherence counselling and text message reminders improved adherence among HIV patients. Its adoption for HIV patient management is advocated. At post-intervention, 76.9% of the intervention group and 55.8% of the control group achieved adherence ([sup] = 5.211, P = 0.022, RR = 0.75 (0.55-0.96), Cohen's w = 0.224). Also, median CD4+ cell count of the intervention group increased from 193 cells/ml to 575.0 cells/ml against 131.0 cells/ml to 361.5 cells/ml in the control group (P = 0.007).
Antiretroviral therapy in Zambia: do partners on ART enhance adherence?	Jones et al., 2014	Journal article	Not specified	Lusaka, Zambia	HIV-positive serocon-cordant heterosexual couples. Couples in which either or both member were on ART	6 Community Health Centres in urban Lusaka, Zambia	Longitudinal Implementation Science study	446	Influence of partners on each other's adherence and compared adherence between couples in which either one or both members were on antiretroviral therapy (ART)	38 (SD± 8)	Not specified	HIV	Nonadherence was defined as any missed doses in the past 2 weeks. A longitudinal multivariable model was used to examine adherence including time (baseline, 6-, and 12- month follow-up), couple medication status (time varying; medication concordant versus medication discordant), and the interaction between time and medication status as predictors of interest.	At baseline, most participants were adherent to their medication (198 of 261 on medication, 76%). The proportion of adherent participants declined to 66% (143 of 217) at 6 months and returned to 70% (136 of 193) at 12-month follow-up. Adherence at baseline was not related to loss to follow up at 6 months (chi-square, χ2 = 1.25, P = .264) or 12 months (χ2 = 0.877, P = .349). Adherence also did not differ between individuals in HIV-sero-concordant and -sero-discordant couples Adherence was not enhanced by having a partner on ART, and that adherence declined over time. Partners on ART may not necessarily provide support for adherence to each other

Clinic-based food assistance is associated with increased medication adherence among HIV-infected adults on long-term antiretroviral therapy in Zambia	Tirivayi et al., 2012	Journal article	2009	Lusaka, Zambia	ART patients receiving food assistance with a control group of non-recipients	Four Lusaka public-sector ART clinics that distributed food rations (Mtendere, Chawama, Kanyama, and George), and four control clinics that did not distribute rations (Bauleni, Chipata, Matero Reference, and Chilenje)	Cohort study	291	Clinic-based food assistance program: comparing ART patients receiving food assistance with a control group of non-recipients	Intervention: 41 (SD±0.8), Control: 40 (SD±0.6)	Female: intervention: 80% (115), control: 73% (107)	HIV	A comparison between ART adherence and the change in weight and CD4+ lymphocyte count between food insecure, HIV-infected Zambian adults on long-term treatment enrolled in a 6-month clinic-based food assistance program versus a matched control group which did not receive assistance.	The provision of food assistance to HIV infected adults on ART improved medication adherence. After 6 months, food assistance recipients (n=145) had higher ART adherence compared to non-recipients (n=147, 98.3% versus 88.8%, respectively; p<0.01). The improvement in adherence rates was greater for participants on ART for less than 230 days, and those with BMI<18.5 kg/m2, a higher HIV disease stage, or a CD4+ lymphocyte count ≤ 350 cells/µl
Community-based Adherence Clubs for the management of stable antiretroviral therapy patients in Cape Town, South Africa: a cohort study	Grimsrud et al., 2016	Journal article	2012-2013	Cape Town, South Africa	Stable ART patients decentralized to community based adherence clubs	Gugulethu CHC-a large primary health care facility typical of urban public sector ART services across the region	Cohort study	2113	Community-Based Adherence Clubs: A CAC was a community-based, CHW led- and nurse-supported model of care supporting groups of 25 to 30 patients. CACs met every 2 months for group counseling, a brief symptom screening, and distribution of prepacked ART.	33.4 (IQR 28.4–29.8)	Female (71%)	HIV	The outcomes of interest in this analysis were LTFU and viral rebound. LTFU was defined as having no visit in the first 12 weeks of 2014, and patients were censored at the date of last contact with either health care service. Viral rebound was defined as a single viral load measurement .1000 copies per milliliter after previous suppression (1000 copies/mL)	94% were retained on ART after 12 months. CAC participation was associated with a 67% reduction in the risk of LTFU (aHR: 0.33, 95% CI: 0.27 to 0.40) compared with community health centre, and this association persisted when stratified by patient demographic and clinic characteristics. During the study period, 3.0% of CAC patients experienced viral rebound

Food assistance and its effect on the weight and antiretroviral therapy adherence of HIV infected adults evidence from Zambia	Tirivayi et al., 2010	Journal article	2009	Lusaka, Zambia	HIV positive patients who are on ART	Four public-sector ART clinics distributed a standardized household food assistance ration	Cross sectional survey and administrative data	314	World Food Programme food assistance program: The WFP country programme aimed to improve the nutritional status and health of vulnerable populations through targeted assistance programs for people living with HIV/AIDS.	intervention: 41 (IQR 39.6-43), control: 40 (IQR 38.7-41.6)	Female: intervention: 80%, control: 71%	HIV	Weight and ART adherence over a period of 6 months among HIV-infected adults	The receipt of food assistance has significant and larger positive effect sizes on adherence to treatment for patients who had been on ART for less than the sample median of 995 days, while food assistance has no effect (ordinary least squares regression) or some negative effect (instrumental variable regression) on adherence for patients whose duration of ART was greater than the sample median
How treatment partners help: social analysis of an African adherence support intervention	O'Laughlin et al., 2011	Journal article	2006-2008	Tanzania	People living with HIV	HIV public care setting	Qualitative study used a grounded theory approach.	40	Partner support	Average age: 40 years	Female (68%)	hiv	Highlights social consequences of treatment partnering and its significance for the health and well being of individuals living with HIV/AIDS in sub-Saharan Africa.	Ninety- eight minimally structured interviews were conducted with twenty pairs of adult HIV/AIDS patients (N = 20) and treatment partners (N = 20) treated at a public HIV-care setting in Tanzania. Four social functions were identified using inductive, category construction and interpretive methods of analysis: (1) encouraging disclosure; (2) combating stigma; (3) restoring hope; and (4) reducing social difference. These functions work to restore social connections and reverse the isolating effects of HIV/AIDS, strengthening access to essential community safety nets. Besides encouraging ARV adherence, treatment partners contribute to the social health of patients. Social health as well as HIV treatment success is essential to survival for persons living with HIV/AIDS in sub-Saharan Africa.

Improving ART adherence among HIV positive adolescents and youth using an eHealth intervention: a field study in Mombasa, Kenya	Ivanova et al., 2019	Journal article	2014 – end 2015	Mombasa, Kenya	HIV positive patients who are on ART	Coast Provincial General Hospital Comprehensive Care Clinic (CCC) and Family Care Clinic (FCC) in Mombasa, Kenya	Cross-sectional study	90	Digital peer support platform aiming at improving adherence to ART treatment among HIV positive youth. The intervention consisted of interactive web-based peer support platform which included a blog with posts written by project coordinators, health care providers and young people on different topics related to sexual and reproductive health, HIV, medication, nutrition, relationships etc.; discussion section; Q&A section with health care providers; stories contest and private messaging. The platform resembled social media platforms with secured users' profiles for	18.4 (SD±2.8) and range:15 to 25 years old	36 were male and 45 were females	HIV	self-reported adherence	the participants were satisfied with the main features of the web platform and stated that they would use it again (95%). However, there was not a significant change in knowledge and behavior, but adherence intentions after 3 months intervention period have improved.

									posting and communication .					
Improving clinic attendance and adherence to antiretroviral therapy through a treatment supporter intervention in Uganda: a randomized controlled trial	Kunutsor et al., 2011	Journal article	2010	Jinja District, Uganda	HIV positive patients who are on ART	Jinja Hospital HIV clinic located in the Jinja District of central Uganda	Two-arm randomized controlled trial	174	Treatment Supporter (TS) intervention designed to improve overall access to ART in the context of resource-limited settings. Patients in the TS arm received both the TS intervention and the standard adherence intervention package. Elements of the standard intervention package consisted of self-monitoring of medication taking using adherence diaries; regular individual and group education by peer-workers using patient education leaflets and tabletop flip-charts; and late	39.1 (SD±8.3)	Female: Treat supporter: 70.1%, non-treat supporter: 65.5%	HIV	Primary outcome measure was medication adherence for both arms of the study as measured by pill counts. Secondary outcomes were mortality, loss to follow-up, and clinic attendance outcomes categorised into attendance on or before day of appointment, within 3 days of appointment day, after 3 days of appointment day, and missed visits.	There was a non-significant difference in mean adherence between the TS and non-TS groups at end of follow-up [99.1% (95% CI: 98.3–99.9% vs. 96.3% (95% CI: 94.2–98.3%), P[0.05]. TS participants had more than four times the odds of achieving optimal adherence (C95%) [Odds ratio (OR) = 4.51, 95% CI: 1.22–16.62, exact P = 0.027]. TS participants were also more likely to be on time for their clinic appointments: 91.6 vs. 90.1% for TS and non-TS, respectively (OR = 1.19, 95% CI: 0.74–1.91, P[0.05). Use of patient-selected treatment supporters may be an effective intervention to improve ARV treatment outcomes in resource-constrained settings.

								attendee tracing. The treatment supporters were usually family members—usually a partner, mother, daughter, sister, brother, friend, or neighbour/friend—who were chosen by the patient with the assistance of the health workers, had accepted the patient's HIV? status and were confidantes.					
Improving treatment adherence for blood pressure lowering via mobile phone SMS-messages in South Africa: a qualitative evaluation of the SMS-text Adherence SuppoRt (StAR) trial	Leon et al., 2015	Journal article	2012-2014	South Africa	Hypertensive patients	A single large public sector clinic in Cape Town, South Africa	A qualitative design using focus groups and in-depth interviews	22	The SMS-text message trial intervention: The intervention was a structured 12-month program of adherence support delivered by SMS-text message, intended to facilitate closer communication between patients and the health care system. Messages were	Age range: 36-78 years old	16 were females and 6 were males	HTN	Self-reported adherence: For the sub-group of participants who reported adherence behaviour change, there are indications that the intervention may have operated in multiple ways to facilitate change	Most participants were comfortable with the technology of using SMS-text messages. Messages were experienced as acceptable, relevant and useful to a broad range of participants. The SMS-content, the respectful tone and the delivery (timing of reminders and frequency) and the relational aspect of trial participation (feeling cared for) were all highly valued. A subgroup who benefitted the most, were those who had been struggling with adherence due to high levels of personal stress. The intervention appeared to coincide with their readiness for change, and provided practical and emotional support for improving adherence behaviour. Change may have been facilitated through increased

								designed to address a range of common potential issues with treatment adherence that might lead to changes in treatment adherence behaviour and improve health outcomes.					acknowledgement of their health status and attitudinal change towards greater self-responsibility.
Integrated mobile phone interventions for adherence to antiretroviral treatment in clients with HIV infection in Accra, Ghana	Dzansi, 2017	Doctoral dissertation	2017	Accra, Ghana	HIV positive patients who are on ART	2 major health facilities Greater Accra	Mixed method: Phase 1- RCT: quantitative analytical experimental study, Phase 2: Qualitative study approach	362	The mobile phone intervention on adherence in two groups (Intervention and Control). The Control group received standard care while the Intervention group received standard care, alarm prompting, weekly text messages and monthly voice calls.	44.4 (SD±9.8)	Female 228 (63%)	HIV	The primary outcome indicator for the intervention was adherence scores. The secondary indicators were BMI, CD4 counts levels. Primary (overall adherence: Self-report, visual analogue, pill identification, pill count) and secondary (CD4 count and Body Mass Index) outcomes were measured at baseline, month three and month six. In phase two, individual interviews were conducted with six clients and two health professionals; three focus group discussions were held with participants from the Intervention group at month six.	Respondents were highly adherent at baseline (n =255, 70%) month three (n =176, 80%) and month six (n = 180, 67%). Overall adherence outcome for the three timelines in the Intervention (M = 99.2, SE = .059, CI = 99.1, 99.4) and Control (M = 99, SE = .066, CI = 98.9, 99.2) groups was statistically significant F (1, 2547) = 4.24, p = .04. The observed change occurred in both groups, therefore not attributable to the treatment. Intervention was rated as helpful and qualitative outcomes show a readiness for integration of mobile phone in care.

Intensive adherence counselling for HIV-infected individuals failing second-line antiretroviral therapy in Johannesburg, South Africa	Fox et al., 2016	Journal article	between 1 March 2012 and 1 December 2013.	Johannesburg, South Africa	Patients on second-line ART	Themba Lethu Clinic-a public-sector clinic in Johannesburg	Single-arm prospective cohort study	400	Intensive adherence counselling for HIV-infected individuals failing second-line antiretroviral therapy. Patients with an elevated viral load (≥400 copies/ml) on second-line are flagged by clinic staff, bypass the normal clinic queue and undergo detailed counselling with an experienced adherence counsellor or social worker trained to address common misconceptions about ART. Counsellors use a standardised form that includes a depression screen, alcohol and substance abuse evaluation, and an assessment to help identify barriers to adherence. The form includes	40.8 (IQR 36.2–46.7)	Female 249 (62%)	HIV	Primary outcome was a suppressed viral load at the first viral load measure after targeted adherence counselling. Follow-up began at the first elevated viral load on a PI and ended at the earliest of death, loss to follow-up, transfer	Of the 400 patients who underwent targeted adherence counselling after an elevated viral load on second-line ART, 388 (97%) underwent repeat viral load testing. Most of these (n = 249; 64%, 95% CI 59–69) resuppressed (400 copies/ml, 11 switched to third line, 5 were awaiting third line, 4 had died and 13 were lost to follow-up. Among the unsuppressed, 48 successfully underwent resistance testing with some resistance detected in most (41/48).

								questions on side effects of medications, the patient's social circumstances, the patient's employment status and depression indicators. All patients also complete a standardised adherence screen.					
Internet and cell phone as tools to support antiretroviral therapy adherence among HIV infected patients aged above 18 years attending Kenyatta national hospital	Kinyua, 2015	Masters degree dissertation	2015	Kenya	HIV infected patients on ART at Kenyatta National Hospital comprehensive care clinic.	Kenyatta National Hospital, Kenya	Descriptive cross-sectional study	385	HIV infected patients received weekly SMS messages from a clinic nurse and were required to respond within 48 hrs. Patients in the control group received standard follow-up without text messages.	mean age: 40.3 years	Females 237 (62%)	HIV	Primary outcomes were self-reported ART adherence (>95% of prescribed doses in the past 30 days at both 6- and 12-month follow-up visits) and plasma HIV-1 viral RNA load suppression	Nearly all (99%) of the HIV infected clients interviewed supported the idea of cell phone use in improving adherence to their medication. Majority (98%) of the xviii respondents reported that internet was not a feasible tool in supporting ARV adherence due to its high cost of maintenance and use. The study concluded that there was higher accessibility of the participants to cell phone than internet and the high usage of cell phones for communication through calling and texting, while high usage of internet for communication through social media networks. Cell phone was identified as a feasible tool for supporting adherence to ARV therapy due to its affordability and easy access. The study therefore recommends adoption of cell phone into health care sector to boost medication adherence.

It helps me live, sends my children to school, and feeds me: a qualitative study of how food and cash incentives may improve adherence to treatment and care among adults living with HIV in Tanzania	Czaicki et al., 2017	Journal article	Interviews were conducted between February and May 2015.	Shinyanga, Tanzania	HIV positive patients who are on ART experiencing food insecurity	Two government hospitals and one government health clinic	Qualitative study	29	Food and cash incentives to improve adherence to ART among food-insecure HIV patients: nutritional assessment and counselling (NAC; control), NAC plus monthly food incentive, or NAC plus cash incentive. Participants in the food or cash arms were eligible for up to 6 monthly incentives of equivalent value conditional on attending routine appointments (within a 4-day window).	Not Specified	16 women and 13 men	HIV	Retention in care and adherence to antiretroviral therapy (ART)	We found that the incentives acted through three pathways to potentially increase retention in care and adherence to ART: 1) addressing competing needs and offsetting opportunity costs associated with clinic attendance, 2) alleviating stress associated with attending clinic and meeting basic needs, and 3) by potentially increasing motivation. Participants did not report any harmful events associated with the incentives but reported myriad beneficial effects on household welfare.
Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders	Pop-Eleches et al., 2011	Journal article	between June 2007 and August 2008	Kenya	Adult patients on ART	Chulaimbo Rural Health Center (CRHC) in Nyanza Province, Kenya.	Randomized controlled trial	431	Mobile phone technologies: four SMS reminder interventions with 48 weeks of follow-up. Participants in the intervention groups received SMS reminders that were either short or long and sent at	Average age: 35.65 (N =137)	Female (66%)	HIV	Adherence was measured using the medication event monitoring system. The primary outcome was whether adherence exceeded 90% during each 12- week period of analysis and the 48-week study period. The secondary outcome was whether there were treatment interruptions lasting at least 48 h.	In intention-to-treat analysis, 53% of participants receiving weekly SMS reminders achieved adherence of at least 90% during the 48 weeks of the study, compared with 40% of participants in the control group (P=0.03). Participants in groups receiving weekly reminders were also significantly less likely to experience treatment interruptions exceeding 48 h during the 48- week follow-up period than participants in the control group (81 vs. 90%, P = 0.03). These results suggest that SMS reminders may be an

									a daily or weekly frequency.					important tool to achieve optimal treatment response in resource-limited settings.
Mobile phone text messages to support treatment adherence in adults with high blood pressure (SMS-Text Adherence Support [StAR]) a single-blind, randomized trial	Bobrow et al., 2016	Journal article	Between June 26, 2012, and November 23, 2012,	Cape Town, South Africa	Hypertensive patients	large public sector clinic in Cape Town, South Africa	A parallel, three-group randomized controlled trial	1372	Two SMS text-messaging based interventions with clinical staff, and patients with high blood pressure working and living in low-income communities around Cape Town.12 The messages were designed to address a range of common issues with adherence to and persistence with treatment.13 We developed a library of SMS-text messages, which we mapped to a taxonomy of	54.3 (SD±11.5)	Sex (male) usual care:126 (28%), information only:126 (28%), Interactive : 127 (28%)	HTN	The primary clinical outcome was the change in mean SBP measured at baseline and twelve months with a validated oscillo metric device,10 adapted to record six sequential readings at three-minute intervals. The mean blood pressure was calculated by discarding the initial reading and calculating the mean from the five remaining readings.	There was a small, reduction in systolic blood pressure control compared to usual care at 12-months. There was no evidence that an interactive intervention increased this effect.1372 participants were randomized to receive information-only SMS text-messages (n=457), interactive SMS text messages (n=458), or usual care (n=457). Primary outcome data were available for 1256 (92%) participants. At 12-months, the mean adjusted change (95% CI) in systolic blood pressure compared to usual care was −2.2 mm Hg (−4.4 to −0.04) with information-only SMS and −1.6 mm Hg (−3.7 to 0.6) with interactive SMS. Odds ratios (95% CI) for the proportion of participants with a blood pressure

									behavior change techniques. Most of the messages focused on the techniques of goals and planning, repetition and substitution, social support, and natural consequences. The SMS text-messages used in the interventions were developed, translated, and tested in English, isiXhosa and Afrikaans, the three languages most commonly spoken by people living in Cape Town.					
Peer mentors, mobile phone and pills: collective monitoring and adherence in Kenyatta National Hospital's HIV treatment programme	Moyer, 2014	Journal article	between 2008 and 2014	Kenya	HIV positive patients who are on ART	Large public sector urban ART outpatient clinic	In-depth ethnographic case study	Not Specified	A text message sent to the designated peer mentor who comes to the Voluntary Counselling center and escorts the HIV patient to the Comprehensive Care Centre, where the file is established, and the client is	Not Specified	Not specified	HIV	No outcome measure	Peer mentors provide counselling services, follow up people who stray from treatment regimens, and perform a range of other tasks related to patient management and treatment adherence

									informed about further laboratory tests and treatment option. The exchange of tele-phone numbers also gave expert clients a way to follow up with the newly diagnosed patients, providing a means of monitoring their health, their entry into medical care, and their adherence. Having the mobile number of a trusted expert client at the treatment centre allowed HIV-positive clients to coordinate the logistical details of hospital visits and drug pick-ups, as well as elicit information and advice about the daily challenges of living with HIV, which spared them additional trips to the clinic.					

Promoting adherence to antiretroviral therapy through a directly administered antiretroviral therapy (DAART) strategy in Mombasa Kenya.	Sarna et al., 2005	Journal article	between September 2003 and November 2004;	Mombasa, Kenya	HIV positive patients who are on ART	Coast Province General Hospital, Mkomani Bomu Clinic, and Port Reitz District Hospital in Mombasa, Kenya	Two-arm randomized controlled trial	234	A directly administered antiretroviral therapy strategy (DAART). The DAART intervention lasted for a period of 24 weeks. During this time, participants in the DAART arm visited a health centre twice a week where they met with DAART observers (nurses) who observed the ingestion of one dose of antiretroviral medications, performed pill-counts, collected used medication bottles, enquired about difficulties encountered, and provided individualized adherence support. At these visits medications were dispensed for the following three or four days, until the next	37 (IQR 20–58)	Female (64%)	HIV	Mean adherence levels compared to those who received standard follow-up. Adherence levels in excess of 95 percent over 24 weeks consistently at each reporting period as compared to those receiving standard follow-up. differences in CD4 counts and weight between the two groups at 24 weeks of follow-up.	Data from pill counts show that mean adherence over 24 weeks was significantly higher in the DAART group compared to the non-DAART group (96 percent vs. 90 percent; p = 0.042). Data from pill counts also show that a greater proportion of DAART clients achieved a total adherence > 95 percent over 24 weeks than non-DAART clients (92 percent vs. 80 percent; p = .012). igh levels of adherence to HAART were observed for all patients during the first 24 weeks of the regimen. However, patients exposed to the DAART intervention achieved higher mean adherence levels compared to those who received standard follow-up. A higher proportion of DAART patients achieved adherence levels in excess of 95 percent over 24 weeks consistently at each reporting period as compared to those receiving standard follow-up.

									visit. During the DAART intervention, community health workers (CHWs) traced participants who missed visits and carried medications home for those who, for reasons of ill-health, were unable to visit the center. After the first 24 weeks, DAART patients were followed by routine monthly visits for a further 48 weeks.					
Real-time electronic adherence monitoring plus follow-up improves adherence compared to standard electronic adherence monitoring	Haberer et al., 2017	Journal article	Participants were drawn from a observational cohort from 2005–2011, followed by real-time EAM from 2011–2015. Cohort enrolment occurred	Uganda	HIV positive patients who are on ART		Ad-hoc analysis of a cohort study	112	In electronic adherence monitoring (EAM), a device records each opening with a date-and-time stamp as a proxy for medication ingestion. Standard EAM devices store these data for later transfer to a computer. EAM was followed subsequently by home visits	Median age: 36 years (IQR not specified)	Females (68%)	HIV	Differences in overall adherence and sustained adherence interruptions between these two periods	Real-time EAM with follow-up triggered by incomplete adherence is an effective intervention. Follow-up visits were not designed as interventions; however, participants likely perceived them as supportive. Immediately after switching from standard EAM to real time EAM plus follow-up, mean adherence increased from 84% to 93%.

			through 2012. Some participants were therefore monitored with both types of EAM; others were monitored only with real-time EAM.						for sustained adherence interruptions.					
Short message service (SMS) reminders and real-time adherence monitoring improve antiretroviral therapy adherence in rural Uganda	Haberer et al., 2016	Journal article	Between September 2013 and October 2014,	Uganda	HIV positive patients who are on ART	Mbarara Regional Referral Hospital in southwestern Uganda	Pilot randomized controlled trial.		All study participants received a real-time adherence monitor and were followed for 9 months. Monitor openings during periods of inadequate cellular reception were stored for later transmission. Participants were given solar chargers and sent an SMS to charge the monitor as needed.	Median age: 31 years (IQR not specified)	Females (65%)	HIV	The primary outcome of interest was adherence (calculated as the number of monitor opening signals received divided by the number of monitor opening signals expected, and capped at 100%). Scheduled SMS reminders improved ART in the context of real-time monitoring. Larger studies are needed to determine the impact of triggered reminders and role of social supporters in improving adherence.	Scheduled reminders were experienced as supportive, whereas triggered reminders could be received too late to be effective (i.e., after participants were asleep) Although prior studies saw significant benefit in overall adherence and adherence lapses with SMS linked to real-time detection of late or missed doses. Potential explanations include the overall high adherence in this study and the small sample size that scheduled SMS significantly increased adherence in individuals initiating ART in Uganda. The technology employed for real-time adherence monitoring and accompanying SMS was successfully implemented despite limited resources.

The Cameroon Mobile Phone SMS (CAMPS) trial: a randomized trial of text messaging versus usual care for adherence to antiretroviral therapy	Mbuagbaw et al., 2012	Journal article	2010-2011	Cameroon	HIV-positive adults on ART (aged 21 years and above)	Yaoundé Central Hospital (YCH) Accredited Treatment Centre (ATC).	Single-site randomized two-arm parallel design trial	200	The use of motivational mobile phone text messages (SMS) to improve adherence to antiretroviral therapy (ART) over six months. A short text message was send to each participant in the intervention (SMS) group, once a week. The content of the message was motivational, with a reminder component. The content was varied and contemporary (e.g. messages would contain season's greetings) so as to retain participants' attention throughout the study period and to explore the various aspects of behavior change. Text messaging was an add-on to usual care that	SMS group: 41.3 (SD±10.1), Control group: 39.0 (SD±10.0)	Female; SMS 69 (68.3%) vs Control 78 (78.8%)	HIV	The primary outcome was adherence measured using a visual analogue scale (VAS), number of doses missed (in the week preceding the interview) and pharmacy refill data. Outcomes were measured at 3 and 6 months. Service providers and outcome assessors were blinded to allocation. To conclude, standardized motivational mobile phone text messages did not significantly improve adherence to ART in this study. Other types of messaging or longer term studies are recommended	Analysis was by intention-to-treat. Between November and December 2010, 200 participants were randomized, with 101 in the intervention group and 99 in the control group. At 6 months, overall retention was 81.5%. We found no significant effect on adherence by VAS>95% (risk ratio [RR] 1.06, 95% confidence interval [CI] 0.89, 1.29; p = 0.542; reported missed doses (RR 1.01, 95% CI 0.87, 1.16; p>0.999) or number of pharmacy refills (mean difference [MD] 0.1, 95% CI: 0.23, 0.43; p = 0.617. One participant in the intervention arm reported a possible disclosure of status.

									includes regular ART counselling and home visits determined on a case-by-case basis. In the control (no SMS) group, participants received only usual care. They did not receive any text messages, but they were interviewed at baseline, 3 months and 6 months.				
THE EFFECT OF ADHERENCE COUNSELLING AND SHORT MESSAGE SENDING (SMS) REMINDERS ON ADHERENCE TO TREATMENT IN CLIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN RIVERS STATE	Maduka, 2011	A dissertation	2011	River state, Nigeria	HIV positive patients who are on ART	Two HAART treatment facilities were selected the University of Port Harcourt Teaching Hospital (UPTH) and the Health of the Sick Catholic Hospital (HOSH) in Port Harcourt.	Experimental study, employing a two site, two group randomized control trial.	104	The effect of adherence counselling and short message sending reminders as interventions to improve adherence to ART. A. Intervention Group: 1.Adherence Counselling: One adherence counselling session per month for four consecutive months was conducted for each client Each session lasted between 45 and 60 minutes. 2.Short	35.94 (SD±14.9), range: 20-68.	Females (56.7%)	HIV	Self-Reported Adherence: This was calculated based on client self-report of number of pills missed in the past seven days. A cut off of 95% was used to distinguish those who were adherent from those who were not. Adherence was assessed at recruitment (before the commencement of the intervention), at every monthly counselling visit and at the end of the intervention in the fourth month. However, the two adherence values used for comparison were the pre-intervention and post intervention	At the end of the intervention period, adherence was significantly higher in the intervention group (76.9%) than in the control group (55.8%) (p=0.022) with a small effect size (Cohen's w) of 0.224 and RR of 0.75 (0.55 to 0.96). In addition, the mean CD4+ cell counts for the intervention group (574.15 cells/ml) was significantly higher than that of the control group (408.58 cells/ml) (p=0.005) with a medium effect size (Cohen's d) of 0.560. The responses from the focus group discussions corroborated the findings from the quantitative analysis and shed light on the perceptions of patients as to the impact of these interventions.

									Message Sending (SMS) reminders Twice a week (Monday and Thursday morning) for the duration of four months, each client enrolled into the intervention group of the study was sent a pre scripted text message containing adherence related information and a reminder to take HAART medications. B. Control group - The control group received standard care only. They did not get any adherence counselling and SMS message reminders.				adherence rates in the intervention and control groups. CD4+ Ce ll Count: Pre and post intervention CD4 cell counts were carried out for all study participants. The results for the intervention and control groups were compared to ascertain any changes in CD4 levels pre and post intervention and the magnitude of such changes if present. CD4 count has been shown to be useful as a biological measure of response to HAART treatment which is dependent among other things on adherence to treatment.	

The effect of food assistance on adherence to antiretroviral therapy among HIV/AIDS patients in Sofala province, in Mozambique: a retrospective study	Posse et al., 2013	Journal article	September 2007 to December 2010)	Sofala province, Mozambique	HIV/AIDS positive patients of all ages, including children, tuberculosis patients and pregnant and breast-feeding women enrolled in prevention of mother-to-child transmission (PMTCT) programs.	Five districts in Sofala province (Beira, Dondo, Nhamatanda, Caia and Muanza) with similar patients, who did not receive food assistance. Controls- from four districts in Zambezia province (Quelimane, Namacurra, Nicoadala and Mopeia).	Retrospective study	357	Provision of food assistance for HIV/AIDS patients in Sofala Province. This intervention was provided to HIV/AIDS patients of all ages, including children, tuberculosis patients and pregnant and breast-feeding women enrolled in prevention of mother-to-child transmission (PMTCT) programs	FA recipients 38.52 (SD±9.06) vs controls 36.61 (SD±10.20)	Female Fa recipients 134 (77.91%) vs controls 125 (67.57%)	HIV	Adherence based on pill pick-up, a pharmacy adherence measure (PAM), which measures whether an individual picks-up all or a majority of their prescribed ART. PAMs are ideally suited to monitoring adherence because they are objective and can be easily derived from data routinely collected for other purposes, such as clinical care or drug supply management	During the food assistance programme, the adherence of food assistance recipients who received food assistance for a period of six and 12 months and non-food assistance recipients is not significantly different as the average impact is only 0.4% (p=0.94) and -2.3% (p=0.73) respectively. For the period after food assistance had been terminated, adherence is still not significantly different between the two groups, as the average impact is 5.3% (p=0.44) and 1.9% (p=0.65).
The Effect of Home Follow Up Visit in Enhancing Antiretroviral Therapy Adherence Among HIV and AIDS Patient in a Rural Setting, Malawi	Mwale et al., 2016	Journal article	from 2009 January to December 2010	Malawi	The study populations were HIV patients, who had been on Triomune (combination of Stavudine, Lamivudine and Nevirapine) continuously for more than one year from the period of being initiated on	St Gabriel's and Kapiri Mission Hospitals in Lilongwe and Mchinji districts, Malawi	An Operational Evaluation Quantitative Descriptive Study	589	Comparing the level of adherence to ART between patients who receive ambulatory treatment at a health facility with a home visit program and those receiving treatment at a health facility without home visit program.	**Not Specified**	Female: St Gabriel's 55 (51%) and Kapiri Hospitals (47%)	HIV	No clear outcome measure documented. Levels of ART adherence in patients who were not attached to treatment helpers were assessed.	The Chi square test results showed that there was a significant difference in the ART adherence between HIV patients who received ambulatory treatment at health facility with no follow up visit (Kapiri) and that of a follow up visit (St Gabriel's). $\chi 2 = 21.02$, p=0.001, α=0.05 with effective size = 0.189. Follow up of clients by treatment helpers within the community can help to improve ART adherence and retention of clients on ART.

					antiretroviral drugs, and were living within the catchment area of the two Mission Hospitals namely St Gabriel's and Kapiri.								
The experience of "medicine companions" to support adherence to antiretroviral therapy: quantitative and qualitative data from a trial population in Uganda	Foster et al., 2010	Journal article	2005-2008.	Uganda	HIV positive patients	AIDS Support Organization (TASO) Clinic in Jinja, southeast Uganda	Randomized controlled trial	1453	Patients were randomized to either home based (HB) or facility based (FB) care, using cluster randomization. Patients receiving HB care visited monthly by a field officer on a motorcycle. HB care patients visit the TASO clinic every six months for a routine clinical and counselling review. FB patients visit the clinic every month to collect drugs and be seen by a nurse; they are assessed routinely every three months by a counsellor and physician.	The mean age of the MCs: 30.8 years and the median is 30 (33.8 for men, 29.5 for women), but the mode is 14)	Female (71%)	HIV	The qualitative study sample was stratified to ensure equal numbers of participants by sex, trial arm, and clinical/ immunological stage contrasting early (CD4 counts above 150106 /l or Stages I and II defining conditions) and advanced (CD4 counts below 100106 /l or Stage III and IV defining conditions) categories. The patients were asked about the role of their MC, how they chose their MC, and how helpful the MC was in their therapy. Textual data on rationales and experiences with MCs were transcribed, translated, coded and analyzed by two independent reviewers. This paper reports on the data collected at baseline. Characteristics of MCs in both arms of the	Women were most likely to choose a child as their MC while men were most likely to choose their spouse; 41% of women chose an MC under 21 compared with only 14% of men. Only 31% of married women chose their husband, compared with 66% of married men who chose their wife. Qualitative interviews suggested MCs proved useful for reminding and other supportive tasks in the first three months but were generally less essential by six months and beyond. Convenience, reliability, and trust were key considerations in choosing an MC. Children provided the only alternative for many unmarried women, but even some married women felt children made more reliable MCs than husbands. Participants who had disclosed their serostatus usually received drug-taking reminders from multiple household members. One participant in the qualitative sample with poor family relations delayed starting treatment due to unwillingness to identify an MC. MCs were generally welcome and useful in supporting early adherence. However, disclosure to

									Patients in both arms visited the TASO clinic any time they felt unwell, and they had access to a telephone hotline. In the FB arm, patients eligible for ART were given Voluntary Testing and Counseling (VCT) vouchers for each family member and for the medicine companion (MC) and were encouraged to bring them to the facility for free VCT. In the HB arm, ART patients were visited by TASO field officers and VCT was provided at their homes to household members and to the MC if requested. All patients were requested to appoint a MC to assist them in remembering to take their medicines and to encourage them when				study, and on the qualitative data about MCs collected through in-depth interviews at baseline, months 3, 6, and 36 (no questions on the MC were asked at the 18th month interview).	an MC should not be a condition of obtaining treatment

									they are not feeling well. In the FB arm, eligible patients were asked to come along with their MCs on their enrolment visit. This was a condition for ART initiation.					

The impact of community- versus clinic-based adherence clubs on loss from care and viral suppression for antiretroviral therapy patients: Findings from a pragmatic randomized controlled trial in South Africa	Hanrahan et al., 2019	Journal article	From February 12, 2014, to May 31, 2015	South Africa	HIV positive patients who are virally suppressed on antiretroviral therapy (ART)	Witkoppen Health and Welfare Centre in Johannesburg, South Africa	Pragmatic randomized controlled trial	775	Adherence clubs, where groups of 25–30 patients who are virally suppressed on antiretroviral therapy (ART) meet for counselling and medication pickup, represent an innovative model to retain patients in care and facilitate task-shifting. This intervention replaces traditional clinical care encounters with a 1-hour group session every 2–3 months and can be organized at a clinic or a community venue. We randomized eligible adults into pairs of clubs—376 (49%) into clinic-based clubs and 399 (51%) into community-based clubs.	median age: 38 years	Female (65%)	HIV	The primary outcome was loss from club-based care, defined as referral to clinic-based standard care for any of the above specified reasons. Participants were assessed for the outcome at each club visit, each annual medical visit and any interim clinical visit made between medical visits. The primary outcome was assessed through review of the club register and review of the participants' clinical files and electronic medical records. Key prespecified secondary outcomes were the proportion of patients who voluntarily chose to return to clinic-based standard care, the proportion of patients with medical contraindication for continuation of club-based care (those referred back to clinic-based care because of pregnancy, TB diagnosis, hypertension, identification of an excluding comorbid or chronic condition, or ART regimen change), and all-cause mortality. Participants were followed for outcomes for 24 months	Overall, 47% (95% CI 44%–51%) experienced the primary outcome of loss from club-based care. Among community-based club participants, the cumulative proportion lost from club-based care was 52% (95% CI 47%–57%), compared to 43% (95% CI 38%–48%, p = 0.002) among clinic-based club participants. The risk of loss to club-based care was higher among participants assigned to community-based clubs than among those assigned to clinic-based clubs (adjusted hazard ratio 1.38, 95% CI 1.02–1.87, p = 0.032), after accounting for sex, age, nationality, time on ART, baseline CD4 count, and employment status. Among those who were lost from club-based care (n = 367), the most common reason was missing a club visit and the associated ART medication pickup entirely (54%, 95% CI 49%–59%), and was similar by arm (p = 0.086). Development of an excluding comorbidity occurred in 3% overall of those lost from club-based care, and was not different by arm (p = 0.816); no deaths occurred in either arm during club-based care. Viral rebound occurred in 13% of those lost from community club-based care and 21% of those lost from clinic-based care (p = 0.051). In post hoc secondary analysis, among those referred to standard care, 72% (95% CI 68%–77%) reengaged in clinic-based care within 90 days of their club-based care discontinuation date. The main limitations of the trial are the lack of a comparison group receiving routine clinic-based standard care

													following the initial treatment assignment, and outcomes were compared by arm.	and the potential limited generalizability due to the single-clinic setting.

The Meanings in the messages: how SMS reminders and real-time adherence monitoring improve antiretroviral therapy adherence in rural Uganda	Ware et al., 2016	Journal article	September 2013 and June 2015	Uganda	HIV positive adult patients who are on ART	Mbarara Regional Referral Hospital (MRRH), Mbarara, in rural southwestern Uganda.	Qualitative study, conducted with a pilot randomized controlled trial.	63	The study investigated the effects of multiple types of SMS reminders combined with real-time adherence monitoring on ART adherence. All study participants were given a real-time adherence monitor and were randomized (1 : 1 : 1) to receive 'scheduled' SMS reminders (daily, weekly), reminders 'triggered' by a missed dose, or no SMS (a control group).	30 (IQR 25-35)	Female (65%)	HIV	Category development began with repeated reviews of coded data to populate one a-priori category (SMS reminder preferences), and to identify emergent themes. Subsequent steps included specifying labels, organizing, and writing descriptions of category content, and supplying evidence from the data in the form of illustrative quotes from interviewees.	SMS reminders prompted taking individual doses of antiretroviral therapy and helped to develop a 'habit' of adherence. Real-time adherence monitoring was experienced as 'being seen'; participants interpreted 'being seen' as an opportunity to demonstrate seriousness of commitment to treatment and 'taking responsibility' for adherence. Both SMS reminders and real-time monitoring were interpreted as signs of 'caring' by the healthcare system. Feeling 'cared about' offset depressed mood and invigorated adherence.

The role of social support on HIV testing and treatment adherence: A qualitative study of HIV-infected refugees in southwestern Uganda	Rouhani et al., 2017	Journal article	from March to July 2011	Uganda	HIV-infected refugees on anti-retroviral therapy (ART) in Uganda	GIZ clinic in Nakivale refugee settlement in Southwestern Uganda	Qualitative study	61	Four roles for the types of social support were identified: (1) informational support encouraged refugees to test for HIV; (2) emotional support helped refugees cope with a diagnosis of HIV; (3) instrumental support facilitated adherence to ART and (4) after diagnosis, HIV-infected refugees provided informational and emotional support to encourage other refugees to test for HIV.	Average agr was 40 years old	Female (59%)	HIV	The categories that emerged fit within four commonly acknowledged types of social support: emotional support, informational support, instrumental support, and appraisal support. Emotional support was defined as the conveyance of love, caring, trust and acceptance. Informational support was information that helped solve problems and explain circumstances, such as advice and suggestions. Instrumental support was tangible and involved the donation of goods and services. Appraisal support involved assistance with self-evaluation. Finally, the data were classified into conceptual categories of social support that the participant received from others (informational support, emotional support, and instrumental support) versus social support the participant offered to others.	Our data indicate that, for refugees in Nakivale on ART, social support has a profound influence on HIV testing and adherence to medications. In our study population, informational support encouraged refugees to test for HIV and thus access care. Emotional support helped patients cope with an HIV diagnosis, and instrumental support helped them adhere to HIV treatment. Additionally, patients felt they could encourage testing by providing informational and emotional support to others. Taken together, our findings suggest that, in Nakivale, social support among refugees plays a similar role in determining HIV testing and treatment adherence compared to non-refugee populations. This similarity does not diminish the importance of these findings but rather suggests an opportunity to explore how social support interventions successful in other settings can be modified to the refugee context. In this study, informational support encouraged patients to test, and the patients in turn offered similar support to encourage others to test. The results of our study suggest that HIV-infected refugees might also encourage testing uptake by making it more salient and acceptable to their social contacts.

The use of a brief, active visualisation intervention to improve adherence to antiretroviral therapy in non-adherent patients in South Africa	Jones et al., 2019	Journal article	May and November 2016	South Africa	Non-adherent HIV positive patients on ART	Two sites in the Western Cape South Africa; Infectious Diseases Clinic at a major peri-urban hospital and a community clinic	Randomized controlled trial	111	The intervention was an active visualisation device. The intervention was delivered by the trained research assistants. The intervention took approximately 10 minutes with each participant. The intervention runs through scenarios to demonstrate that medication must be taken each day, as even when medication is added to the 'body', the following day the pink colour returns because the infection cannot be reversed. This process demonstrates why consistent adherence is needed to achieve virological suppression. The intervention also demonstrates	Mean: 36.48 (SD±9.66), range: 15 to 59 years	Female (75/11, 67.6%)	HIV	The primary outcome was adherence as measured by plasma viral load (VL).	There was a clinically significant difference (p=0.06) in VL change scores between groups from baseline to follow-up, where the intervention had a greater decrease in log VL (Madj=−1.92, CI [−2.41, −1.43), as compared to the control group (Madj=−1.24, [−1.76, −0.73]). Participants in the intervention group were also significantly more likely to have a 0.5 log improvement in VL at follow-up (χ2(1)=4.82, p=0.028, ϕ=0.28).

								the effects of missing one or two doses of ART, versus how long-term non-adherence can lead to treatment failure.					
Treatment partners and adherence to HAART in Central Mozambique	Stubbs et al, 2009	Journal article	between September 2004 and June 2006	Mozambique	HIV positive patients on ART patients with good adherence and suboptimal adherence	Beira Day Hospital pharmacy, Mozambique	Randomized controlled trial	896	Treatment partners: Prior to starting HAART, patients are encouraged to self-select a treatment partner, such as a spouse, family member, or friend. If a treatment partner cannot be identified, clinic staff may suggest a treatment partner who is either a peer counsellor based in the clinic or a member of a community-based group of people living with HIV/AIDS.	15 - 29 (24.5%), 30-39 (40.6%), 40-49 (24.2%), 50> (10.7%)	Female (54.2%)	HIV	Adherence rates was calculated based on pharmacy records for all patients who refilled their medication for at least six consecutive months between September 2004 and June 2006. Differences in baseline characteristics for patients with high (≥90%) adherence versus patients with low (<90%) adherence were assessed to identify factors that may be associated with high and low adherence, respectively, in this study population	A total of 305 patients (70%) had self-selected treatment partners, 121 (28%) had community-based treatment partners, and 8 (2%) had no treatment partner. In adjusted analysis, patients who had no treatment partner were more likely to have low adherence (OR 9.47; 95% confidence interval 2.37–37.86 compared to self-selected treatment partner). Patients with community-based treatment partners did not have significantly lower adherence than patients with self-selected treatment partners.

Treatment supporter to improve adherence to antiretroviral therapy in HIV-infected South African adults: a qualitative study	Nachega et al., 2006	Journal article	July 1 to August 30, 2004	South Africa	HIV positive adult patients who are on ART	HIV primary care settings: 3 clinics in Khayelitsha and 1 clinic in Gugulethu	Exploratory qualitative pilot study	19	This study aimed to understand how patient-selected treatment supports might affect antiretroviral treatment outcomes and to identify key components of support, including the social and material resources necessary for promoting high adherence in South Africa.	Range: 22-42 years	Female 11, Male 1	HIV	Information was collected from patients (insiders) and health care providers (outsiders) involved in HAART programs to determine the characteristics of effective treatment support and to learn more about social and material barriers to HAART adherence. The transcripts were used for content analysis to identify main themes and were then coded for retrieval and analysis. The data collected from the key informants and from the focus groups was based on participants' critical forms and sources of support that facilitate adherence and the social and material barriers that they believe can impede adherence.	The patients and health care workers identified individuals-usually a mother, daughter, sister, brother, or partner-who were confidantes and had moral authority with them. These individuals command respect, and patients allow them to influence health-related decision making, both of which are necessary if they are to be effective treatment supporters. Barriers to adherence identified by study participants include alcohol abuse, stigma related to disclosure of HIV status, and lack of financial resources and food. These are critically important challenges to address if high adherence is to be achieved in this setting. In addition, our results suggest that interventions tailored to treatment supporter characteristics and relationship factors may be effective in influencing patients' antiretroviral therapy adherence
Family support, medication adherence and glycaemic control among ambulatory type 2 diabetic Nigerians in a primary care clinic in	Iloh et al., 2018	Journal article	from April 2011 to Decembe r 2011	Nigeria	Type 2 diabetic Nigerians who were on treatment for at least 3 months at the primary care clinic	Primary care clinic of a tertiary hospital in Nigeria	Descriptive study	120	The role of family support in medication adherence and glycaemic control among ambulatory Type 2 diabetic patients in a primary care clinic in Nigeria. Family support and medication adherence	Range: 27-81 years	Females (62.5%)	DM	Medication adherence was assessed by the use of pretested, interviewer administered questionnaire on 30 days self-administered and reported therapy (SAT). Patients were seen at the recruitment visit and at the end of the study visit. At the end of study visit, the	The age of the participants ranged from 27 to 81 years, and there were 37.5% males and 62.5% females with sex ratio of 1:1.7. Family support, medication adherence, and glycaemic control rates were 77.5%, 72.5%, and 61.7%, respectively. Family support was significantly associated with elderly age (0.041), medication adherence (P = 0.038), and glycaemic control (P = 0.027). The most significant demographic predictor of family support was elderly age (odds ratio

Eastern Nigeria								were assessed in the previous 3 months and 1 month preceding the study using multi-dimensional Scale of Perceived Social Support and interviewer-administered questionnaire on self-administered and reported therapy (SAT), respectively. Glycaemic control was assessed in the previous 1 month.				adherence section of the data collection tool was administered. The details of the information collected had been explained in specific details in the previous study by the authors. Grading of adherence was done using an ordinal scoring of 0–4 points designed by the researchers from literature review as follows: all times = 4 points, most times = 3 points, sometimes = 2 points, rarely = 1 point, and never = 0 point.	= 4.30 [2.06–5.15]; P = 0.015). The elderly patients with Type 2 diabetes were four times more likely to have family support compared to their counterparts who were <60 years.
Role of Family support in medication adherence in Type 2 Diabetes Mellitus patients at an outpatient setting in Nigeria: A prospective cohort study. Affiliation: 1St. Nicholas Hospital, Lagos	Adedigba et al., 2019	Journal article	Between January and April 2016	Nigeria	Patients with type 2 diabetes mellitus	Outpatient Department of Bingham University Teaching Hospital, Jos, Nigeria	Prospective cohort study	132	The influence of family support on medication adherence by comparing medication adherence among patients with good and poor family support using a prospective cohort design. T2DM patients were recruited by systematic random sampling and allocated to two groups	Mean age: 60.6 (SD±11.3). For the good family support group: 58.8 (SD±10.6) years and in the poor family support group: 62.1 (SD±12.0)	Female: 80 participants Male:52 participants	DM	Medication adherence scores were among the study participants comparing medication adherence scores at baseline, 4 weeks, and at eight weeks	Medication adherence scores were generally low (5.54±1.7) among the study participants. Respondents had comparable medication adherence scores at baseline (p =0.39) and 4 weeks (p =0.75), but the difference was significant at eight weeks (p =0.01). Multiple logistic regression showed that good family support (OR 2.042; 95% CI 1.219-3.420; p =0.007), age group 45 to 54 years and age group 55-64 years (OR 3.084; 95% CI 1.113-8.543; p =0.03) were significant predictors of good medication adherence. Good family support is a significant predictor of good medication adherence among type 2 diabetes mellitus patients.

									based on family support scores.					
EFFECTS OF TWO HEALTH EDUCATION INTERVENTIONS ON ADHERENCE TO ANTIHYPERTENSIVE MEDICATION AND ON BLOOD PRESSURE IN SELECTED TERTIARY HEALTH FACILITIES IN SOUTHWESTERN NIGERIA	Atulomah, 2014	Thesis	2013	Nigeria	Hypertensive patients	Patients receiving care in hypertensive clinics in three tertiary health institutions. Intervention 1 (Olabisi Onabanjo University Teaching Hospital, Sagamu), Intervention 2 (Lagos University Teaching Hospital, Lagos) and Control (University College Hospital, Ibadan)	Quasi-experimental	180	Patient Education and Counselling (Intervention 1) and Patient Education and Counselling with Family-Support (Intervention 2) were implemented for four weeks.	Intervention 1; 52.1 (SD±6.5), Intervention 2; 51.3 (SD±7.2) and control group 50.8 (SD±6.2)	Intervention 1, Intervention 2 and control group sexes; Females (28.3%; 41.7%; 38.3%)	HTN	Adherence: Self-Reported Medication Adherence (SRMA), Pill-Count (PC), Appointment Keeping (AK) and Blood Pressure (BP) measurement constituted the outcome variables in this study. SRMA were operationalized in the questionnaire and asked questions about "frequency of forgetting to take prescribed medications", "frequency of deciding not to take medications for the treatment of hypertension", "too busy to take medication" and "frequency of getting refill prescription when medications runs out". Similarly, three questionnaire items were used to measure AK: "frequency of forgetting to go for an appointment", "too busy to meet scheduled appointment with healthcare giver", with reversed coding on "frequency of meeting scheduled appointment". Blood pressure was measured	At baseline, there were no significant differences in outcome measures among the three groups in respect of primary outcomes of SRMA and secondary outcomes of SBP values respectively. At 13th week follow-up, Intervention 2 demonstrated significantly higher scores in respect of SRMA, PC, AK with SBP reduction from compared with Intervention 1 with SRMA and a corresponding SBP reduction. The values of SRMA, PC and AK in control were 9.6±1.0, 59.6±0.6 and 5.8±1.0 respectively with SBP reduction. Furthermore, the magnitude of changes between outcome measures at 13th week follow-up and their respective baseline values for the three groups. Intervention 2 results were significantly higher

													using a mercury sphygmomanometer calibrated in mm of mercury (Hg). Pill-Count was performed by counting pills that were not consumed and subtracting this from total pills prescribed to derive pills consumed during a designated period of 14 days.	
Effect of health literacy on medication adherence among diabetic patients.	Olorunfemi, 2018	Journal article	Not specified	Nigeria	Diabetic patients	University of Benin teaching hospital, state hospital, and Faith Mediplex hospital Benin-city, Edo state, Nigeria.	Correlational research design	180	The correlation between health literacy and medication adherence among Diabetic patients. The participants were asked to fill the research instrument on 1) Morisky Medication Adherence test to find out the level of medication adherence among diabetic patients, 2) Demographic data to determine personal information of the participants and 3) Functional Health Literacy in Adults (TOHFLA) test to determine	Mean age was 57.18 (SD±14.15), median= 60, mode =75	80 (44.4%) male and 100 (55.6%) female	DM	A correlation between health literacy and medication adherence among diabetic patients was explored. The instrument used was Morisky Medication Adherence Scale (MMAS-8) and Short Functional Health Literacy in Adults Test (STOHFLA). Patients with medication adherence of score zero (0) were rated as higher adherence, 1-2 score of medication adherence were rated as average adherence and 3-8 score of medication adherence were rated as Poor adherence, while health literacy score of 1–16 were taken as inadequate and score of 17 and above were taken as Adequate health literacy.	The findings showed that 100 (55.6%) of the participants had low adherence level, 70(38.9%) had medium adherence level and 10(5.6%) of the participants had higher adherence level. It was also found that 33.3% of the participants had adequate health literacy and 66.7% of the participants had inadequate health literacy. The correlation showed that health literacy with p- value of 0.05 is statistically significant to medication adherence.

								the level of acquiring diabetes-related information among diabetes patients in the identified hospitals.					
Role of social support on adherence to antiretroviral therapy among patients attending AMPATH clinic at Moi Teaching and Referral Hospital, Eldoret, Kenya	Kaguiri, 2014	Thesis	Data was collected between January and March 2010.	Kenya	HIV positive adult patients who are on ART	Health Care (AMPATH) clinic-Moi Teaching and Referral Hospital (MTRH) in Eldoret	Cross sectional study	108	Social support was identified as a intervention to improve adherence. This study sought to estimate proportions of patients reporting optimum adherence to ARVs, to identify the types of social support being utilized by AMPATH patients and to determine the association between social support and adherence to ARVs	32 (IQR 28-39)	Males (36.1 %)	HIV	Adherence to HAART was measured by self-report using structured interview questions. The Adult AIDS Clinical Trials Group (AACTG) adherence instrument was used and consists of nine questions that assess adherence. The instrument also assesses reasons for non-adherence. Non-adherence was defined as having missed at least one dose during the past 4 days. Adherence to scheduling was measured by the question "Most anti-HIV medications need to be taken on a schedule, such as '2 times a day' or '3 times a day' or 'every 8 hours.'	Optimum adherence was reported by 219(73.2%) of the participants. Those aged 25- 34 years were more likely to adhere compared to those aged below 25 years (Adjusted OR=3.36, 95% CI: 1.44 – 7.81, P = 0.005). Females were more likely to adhere (Adjusted OR=2.80, 95% CI: 1.45 – 5.38, P = 0.002). Most of the participants (184, 61.5%) reported to be members of support groups, 190(63.5%) reported to have disclosed their HIV status to their sexual partners and advice from health care providers was reported by all the participants. Reporting optimum adherence was positively associated with disclosure of HIV status to sexual partner (Adjusted OR= 2.43, 95% CI: 1.37 – 4.29 P value= 0.002), belonging to a support group (Adjusted OR=2.68, 95% CI: 1.51 – 4.76, P value = 0.001) and perceived support from children (Adjusted OR=2.90, 95% CI: 1.29 – 6.53, P value = 0.01).
Perceived family support and factors influencing medication adherence among hypertensive	Olowookere et al., 2018	Journal article	Not specified	Nigeria	Hypertensive patients	Medical Outpatient Clinic of Federal Medical Centre Owo, Ondo State, Nigeria.	Descriptive cross-sectional study.	420	This descriptive cross-sectional study assessed perceived family support and other factors that determine medication	60.6 (SD±11.7) years, range: 21-85 years.	Females: 214 (51%)	HTN	The relationship between family support and adherence to drug treatment amongst hypertensive outpatients was explored. Degree of adherence by individual patients was	Most respondents were Yoruba (86.2%), married (76.7%), and had primary education (27.6%). Most (61%) were adherent to antihypertensive therapy. Common reasons for poor adherence include belief of cure (43%), high cost of treatment (33%), and the experiencing of side effects (27%).

patients attending a Nigerian tertiary hospital									adherence among hypertensive patients in a tertiary hospital.				estimated manually by means of patient self-report. The degree of adherence from patient self-report was estimated using the number of pills prescribed minus the number of pills missed over number of pills prescribed. From the formula, level of adherence by individual patients was categorized into those with less than 80% adherence and those with equal to or more than 80% adherence. Adherent patients were defined in this study as individuals with at least 80% adherence level.	Patients with good family support had better adherence compared to those with poor family support ($P < 0.05$).
"They just come, pick and go." The Acceptability of Integrated Medication Adherence Clubs for HIV and Non Communicable Disease (NCD) Patients in Kibera, Kenya	Venables et al., 2016	Journal article	Jan-March 2015	Kenya	HIV and Non-Communicable Disease (NCD) patients	Kibera South Clinic, Kenya	Qualitative study	106	We conducted a qualitative research study to assess patient and health-care worker perceptions and experiences of MACs in the urban informal settlement of Kibera, Kenya. A total of 106 patients (with HIV and/or other NCDs) and health-care workers were purposively	Average age: 48 years	Female (64%)	HIV AND NCDs	Key themes around the acceptability and perceptions of MACs were compared across focus group discussions, interviews and participant observation. All transcripts and fieldnotes were coded through an iterative process that involved firstly coding the text into broad themes, then grouping these together and developing sub-themes. Emphasis was placed on comparing the perspectives of HIV positive and NCD	MACs were considered acceptable to patients and health-care workers because they saved time, prevented unnecessary queues in the clinic and provided people with health education and group support whilst they collected their medication. Some patients and health-care workers felt that MACs reduced stigma for HIV positive patients by treating HIV as any other chronic condition. Staff and patients reported challenges recruiting patients into MACs, including patients not fully understanding the eligibility criteria for the clubs. There were also some practical challenges during the implementation of the clubs, but MACs have shown that it is possible to learn from ART provision and

									sampled and included in the study. Ten focus groups and 19 in-depth interviews were conducted, and 15 sessions of participant observation were carried out at the clinic where the MACs took place. Thematic data analysis was conducted using NVivo software, and coding focussed on people's experiences of MACs, the challenges they faced and their perceptions about models of care for chronic conditions.				patients, as well as MAC-members and non-MAC members, to see if they had differing experiences of MACs.	enable stable HIV and NCD patients to collect chronic medication together in a group.
The Influence of Family/Social Support on Adherence to Diabetic Therapy	Affusim, 2018	Journal article	Not specified	Nigeria	Adults diabetic patients	Outpatient clinic of a tertiary health facility in a rural area of Edo state, Nigeria	Descriptive cross-sectional study.	158	Family/Social Support: The Multidimensional Scale of Perceived Social Support (MDSPSS) was used to assess the level of social support the respondents receive from family and friends. The	56 (SD±11.5) years, with most of the respondents (63.9%) aged 46-65 years	Females (53.8%)	DM	Adherence to medication was assessed using the Morisky Medication Adherence scale-8 (MMAS). This tool is an 8-item medication adherence questionnaire. Each item is scored either 1 (for Yes answer) or 0 (for No answer). The total score ranges from 0 to 8. Those with aggregate score of 0	About 48.8% were found to have high social support, 40.5% had moderate support, while 10.8% had low social support. Most of the respondents (70.9%) had low adherence, 19.6% had moderate adherence, while 9.5% had high adherence. There was the significant association between social support and medication adherence, social support, and clinic attendance, social support and BMI, but no significant association between social support and blood sugar level. Since social

									Morisky Medication Adherence Scale-8 (MMAS) was used to assess the level of adherence to medication. Data were collated and analyzed using the IBM-SPSS version 21.0				were regarded as having high adherence, those with 1-2 score were regarded as having moderate adherence and those with 3-8 score were regarded as having low adherence. The level of support that the participants receive from their family, friends and special persons in their lives was assessed using the Multidimensional Scale of Perceived Social Support (MDSPSS). This tool contains 12 items and each is scored between 1 and 7. The total score is derived from dividing the sum across all 12 items by 12. The aggregate score is thus from 1 to 7. Those with aggregate score of 1-2 were regarded as having low support, those with aggregate score of 3-5 were regarded as having moderate support, while those who had an aggregate score of 5.1-7 were regarded as having high support.	support can predict health-promoting behavior, it can also predict self-care behavior of patients with DM. Therefore, getting the family members, especially the spouse, involved in self-care behavior can be of significant importance in providing health care to patients with diabetes.

The Relationship between Family Support and Medication Adherence among Hypertensive Patients in Kenya	Xiong, 2018	Master thesis	unknown	Kenya	Hypertensive patients	Three healthcare facilities in Nairobi, Kenya	Mixed-method cross-sectional study	104	Family support and medication adherence among hypertensive patients in Kenya. Fisher's exact test and Chi-square test were used to compare the level of medication adherence and family support among different subgroups of patients; bivariate logistic regression was used to determine the predictors of medication adherence; and multiple logistic regression was used to examine the independent association between family support/function and medication adherence. Grounded theory was used to guide the thematic analysis of the qualitative data.	56.61 (SD±11.70)	Female (n = 71, 68.27%)	HTN	The medication adherence measurements not specified. Descriptive statistics were used to describe the patient profiles; Test of associations were used to compare the level of medication adherence and family support among different subgroups of patients. Logistic regression was used to determine the predictors of medication adherence; and to examine the independent association between family support/function and medication adherence. Grounded theory was used to guide the thematic analysis of the qualitative data.	The overall control rate of HTN among the patients was low, with only 33.98% of them under control. The percentage of highly adherent patients determined by the Morisky Green Scale was 55.77% and was 26.92% as determined by the Hill-Bone Scale. Based on the Perceived Social Support from Family Scale, most of the patients (82.69%) reported strong family support. The majority of patients (77.88%) were determined to have "functional" families by the Family Function APGAR Scale, and 22.12% had dysfunctional families. Both the bivariate logistic regression and multiple logistic regression generated non-significant results for the association between family support/function and medication adherence using either scale.

Cash vs. food assistance to improve adherence to antiretroviral therapy among HIV-infected adults in Tanzania	McCoy et al., 2017	Journal article	December 2013-July 2015. Participants were prospectively followed for 12 months.	Shinyanga, Tanzania	HIV positive patients who are on ART experiencing food insecurity	Three facilities (two hospitals and one peri-urban clinic) in Shinyanga, a resource-limited region in Tanzania	Randomized controlled trial	805	Nutrition assessment and counselling (NAC) and cash transfers (~$11/month, n = 347), NAC and food baskets (n = 345), and NAC-only (comparison group, n = 113). Cash or food was provided for 6 or less consecutive months, conditional on visit attendance.	35 (IQR 29–43)	Female 509 (64%)	HIV	The primary outcome was medication possession ratio (MPR ≥ 95%) at 6 months. Secondary outcomes were appointment attendance and loss to follow-up (LTFU) at 6 and 12 months.	The primary intent-to-treat analysis included 800 participants. Achievement of MPR ≥ 95% at 6 months was higher in the NAC + cash group compared with NAC-only (85.0 vs. 63.4%), a 21.6 percentage point difference [95% confidence interval (CI): 9.8, 33.4, P < 0.01]. MPR ≥ 95% was also significantly higher in the NAC + food group vs. NAC-only (difference = 15.8, 95% CI: 3.8, 27.9, P < 0.01). When directly compared, MPR ≥ 95% was similar in the NAC + cash and NAC + food groups (difference = 5.7, 95% CI: -1.2, 12.7, P = 0.15). Compared with NAC-only, appointment attendance and LTFU were significantly higher in both the NAC + cash and NAC + food groups at 6 months. At 12 months, the effect of NAC + cash, but not NAC + food, on MPR ≥ 95% and retention was sustained.
Adapting an adherence support workers intervention: engaging traditional healers as adherence partners for persons enrolled in HIV care and treatment in rural Mozambique.	Audet et al., 2017	Journal article	March to July 2016	Mozambique	Traditional healers and HIV positive persons enrolled in HIV care	Rural Mozambique	Qualitative study	180	Adherence support workers intervention: Researchers chose the Adherence Support Workers program, developed by FHI 360, to provide an optimal foundation for our intervention. The Adherence Support Workers program	40 (IQR 28-51)	Female 71 (66%)	HIV	Framework analysis was used to identify main themes from our FGDs about the drivers, core facilitators, and barriers to acceptability of the traditional healer-based intervention approach. Four code maps were developed to categorize data: social, structural, and informational drivers, facilitators, and barriers to acceptability of healers as adherence partners; educational and counselling strategies that healers could use	Traditional healers were an acceptable group of community health workers to assist with patient adherence and retention. Traditional healers, clinicians, and interested community members suggested novel strategies to tailor the adherence support worker intervention, revealing a local culture of HIV denialism, aversion to the health system, and dislike of healthcare providers, as well as a preference for traditional treatments. Proposed changes to the intervention included modifications to the training language and topics, expanded community-based activities to support acceptability of an HIV diagnosis and to facilitate partner disclosure, and accompaniment to

									includes three primary activities: (1) education and psychosocial support to PLHIV initiating/continuing ART; (2) referrals to specialized clinics as needed; and (3) participation of support workers as members of the ART clinical team.				to encourage retention in care and adherence to ART (e.g., partner counselling); the role that healers could play in ensuring that respectful care is provided by clinicians; and recommendations for the development of a "best practice" intervention strategy, including the necessary information, motivation (for healers and PLHIV), and appropriate behavioral considerations healers would be required to follow.	the health facility by healers to encourage delivery of respectful clinical care. PLHIV, healers, and clinicians deemed the intervention socially acceptable during focus groups. We subsequently recruited 180 newly diagnosed HIV-infected patients into the program: 170 (94%) accepted.
The effectiveness of social resource intervention to promote adherence to HIV medication in a multidisciplinary care setting in Kenya.	Kamau et al., 2012	Journal article	Not specified	Kenya	Small-scale farmers, and petty trade or casual labourers who worked in tea, coffee and flower plantations and were HIV positive patients who were prescribed ART	Nine satellite centres under the auspice of the Nazareth Hospital in Kenya	Cross-sectional design	354	The comprehensive HIV treatment and care programme (intervention) encompasses treatment preparation sessions, individual and group counselling, assignment of treatment partners to new patients at the start of HIV treatment, and the provision of the necessary social resources.	18 30, 21.8% 31 40, 43.5% 41 50, 26.8% 51 –64, 7.9%	Female (71.4%)	HIV	Adherence to HIV medication was defined as the correct consumption of all doses and pills at the correct timings, and following all other instructions provided for in the previous four days. A four-day self-assessment period was selected because patients' recall for self-reported adherence is better for shorter periods, when compared with longer periods such as 28 days or more. Any patient who missed any dose, pill or failed to follow proper timing guidelines or other instructions was categorized as non-	Binomial logistics were used to test the relationships between social support and its dimensions with adherence to HIV medication. Composite social support was predictive of adherence to HIV medication (P ,0.05). Among the four dimensions of support, material and emotional support were the strongest predictors.

													adherent. The measure also included 13 items to determine patients' reasons for failing to follow the medication schedule correctly.	
Individualised Motivational Counselling to Enhance Adherence to Antiretroviral Therapy is not Superior to Didactic Counselling in South African Patients: Findings of the CAPRISA 058 Randomised Controlled Trial.	Van Loggerenberg et al., 2015	Journal article	Between August 2007 to February 2009	South Africa	HIV positive adults eligible to initiate ART (at the time, a CD4 T-cell count of 350 or less).	CAPRISA eThekwini HIV-TB clinic, in Durban, South Africa.	Parallel group (1:1 ratio), open label randomised controlled trial	297	On determination of ART eligibility, all patients received two pre-initiation 20–45-minute didactic counselling sessions as standard at the clinic. The didactic arm participants received the final 20–45-minute didactic counselling session only. The motivational counselling arm participants instead received the first 30–40-minute individualised motivational counselling session, and then the additional four individualised motivational counselling sessions at intervals up to	mean 35.8 years	Male (43.1%)	HIV	The primary outcome was the proportion of participants with suppressed viral load (plasma viral load of <400 copies/ml, HIV-1 RNA-PCR – Roche Diagnostics) at nine months (range of eight to 10 months) post-initiation of ART. A secondary outcome looked at adherence by pill count over the previous inter-visit period at six months post-initiation of therapy. Pill count was expressed as a percentage of the pills taken as prescribed over the study visit interval (usually the previous 28 days), by assuming that all non-returned pills had been taken over the study visit interval. These data were verified from the clinic records based on previous study visit and drugs dispensed by the pharmacy. This measure was recorded at 6 months, as this was part of the counselling intervention study follow-up. Suppressed	We randomised 297 HIV-positive ART-naïve patients in Durban, South Africa, to receive either didactic counselling, prior to ART initiation (n=150), or an intensive motivational adherence intervention after initiating ART (n=147). Study arms were similar for age (mean 35.8 years), sex (43.1% male), CD4+ cell count (median 121.5 cells/µl) and viral load (median 119 000 copies/ml). Virologic suppression at nine months was achieved in 89.8% of didactic and 87.9% of motivational counselling participants (risk ratio [RR] 0.98, 95% confidence interval [CI] 0.90-1.07, p=0.62). 82.9% of didactic and 79.5% of motivational counselling participants achieved >95% adherence by pill count at six months (RR 0.96, 95%CI 0.85-1.09, p=0.51).

									six months after initiation of therapy. All participants were followed up to at least nine months on treatment. The standard didactic counselling consisted of three sessions. The first session covered stigma and discrimination, nutrition and taking control of the treatment regimen. The second session focused on HIV pathogenesis, routes of infection, HIV testing techniques, and a basic introduction to ART. The final session focused on information relating to ART, the drug regimen, the importance of adherence, side effects, and the importance of monitoring and the development of resistance.				viral load at 12 months was assessed as an additional secondary outcome.	

How community ART delivery may improve HIV treatment outcomes: Qualitative inquiry into mechanisms of effect in a randomized trial of community-based ART initiation, monitoring and re-supply (DO ART) in South Africa and Uganda	Gilbert et al., 2021	Journal article	2016-2019	western Uganda and KwaZulu-Natal South Africa	HIV positive patients who are on ART	Two peri-urban sites in KwaZulu-Natal, South Africa, and one site in rural Sheema District, in southwest Uganda.	A qualitative study with a three-arm randomized trial of community ART initiation.	150	The Delivery Optimization for Antiretroviral Therapy (DO ART) Study offered ART initiation, monitoring and refills in communities to clinically stable adults living with HIV and not taking ART at the time of enrolment or within the previous 3 months. (1) community-based ART initiation, monitoring and re-supply via mobile vans; (2) clinic-based ART initiation with community-based monitoring and re-supply ("hybrid" services); and (3) clinic-based ART (standard of care).	56% between 30 and 49 years	Female (49%)	HIV	Individual participants' experiences of receiving ART in the community were summarized and entered into a matrix. The matrix both preserved the coherence of individual experiences and helped to identify patterns that cut across the data, for a thematic analytic approach. Thematic concepts identified through the matrix were elaborated through coded data. Coded data corresponding to these concepts were retrieved, revised and added to the thematic concepts. The revised concepts were then labelled, described and illustrated to form descriptive categories. By employing this combined thematic and content analytic approach, a set of categories representing a variety of potential mechanisms was set based on the perspectives and priorities of DO ART Study participants.	The analysis yielded four potential mechanisms drawn from qualitative data representing the perspectives and priorities of DO ART participants. Empowering participants to schedule, re-schedule and select the locations of community-based visits via easy phone contact with clinical staff is characterized as flexibility. Integration refers to combining the components of clinic-based visits into single interaction with a healthcare provider. Providers" willingness to talk at length with participants during visits, addressing non-HIV as well as HIV-related concerns, is termed "a slower pace". Finally, increased efficiency denotes the time savings and increased income-generating opportunities for participants brought about by delivering services in the community.

The Treatment Ambassador Program: A Highly Acceptable and Feasible Community-Based Peer Intervention for South Africans Living with HIV Who Delay or Discontinue Antiretroviral Therapy	Katz et al., 2021	Journal article	2017	South Africa in Gugulethu township	HIV positive people who are not on ART	Community based in Gugulethu township	Randomized controlled trial of an intervention	84	Treatment ambassador program (TAP). Core intervention components included one-on-one client-cantered counselling sessions and patient navigation. TAP was hypothesized to work through several mechanisms and levels as framed by the TTI: (1) individual-level factors, including attitudes and beliefs about treatment, by building the knowledge base and trust of treatment for participants, while promoting self-efficacy and effective coping strategies; (2) social-level factors through social interactive processes that address HIV-related stigma and the need	median age: 43 years	Female (77%)	HIV	Survey measures were administered at baseline and follow-up to assess psychosocial characteristics, as well as sociodemographic and medical characteristics potentially related to behavior at baseline and at follow-up in both arms of the study to evaluate the moderators and mediators of intervention effects. The Theory of Triadic Influence (TTI) states that health related behaviours are shaped by individual-, social-, and structural-level factors and thus, the survey attempted to analyze barriers at these three levels.	TAP was highly feasible (90% completion), with peer counsellors demonstrating good intervention fidelity. Post-intervention interviews showed high acceptability of TAP and counsellors, who supported autonomy, assisted with clinical navigation, and provided psychosocial support. Intention-to-treat analyses indicated increased ART initiation by 3 months in the intervention vs. control arm (12.2% [5/41] vs. 2.3% [1/43], Fisher exact p-value = 0.105; Cohen's h = 0.41). Among those previously on ART (off for > 6 months), 33.3% initiated ART by 3 months in the intervention vs. 14.3% in the control arm (Cohen's h = 0.45). Results suggest that TAP was highly acceptable and feasible among PWH not on ART.

								for disclosure; and (3) structural-level factors through facilitating engagement with clinic providers. the full intervention consisted of eight sessions over 8–14 weeks for people living with HIV who had not initiated treatment within 6 months of testing or had previously initiated ART but been off treatment for over 6 months.					
Those People Motivate and Inspire Me to Take My Treatment. Peer Support for Adolescents Living With HIV in Cape Town, South Africa	Rencken et al., 2021	Journal article	2016 and 2017	Cape Town, South Africa	Adolescents living with HIV who are on ART	A large public hospital in Cape Town, South Africa	Qualitative study with in-depth interviews	35	ALHIV peer support group	Median age: 15 years (range:12-19 years)	19 female and 16 male	HIV	The analysis and outcome for this paper is based on the codes associated with the domain of 'barriers to and facilitators of adherence.' Thematic analysis using an iterative process detailed the codes and nodes through an inductive process (to finalize the codebook). Overall, the study explored (1) barriers and facilitators of adherence, including stigma, fears about HIV disclosure, and access	Three themes emerged: (1) peer support encouraged adherence to ART, (2) serostatus disclosure outside the family was perceived as difficult, and (3) the peer support group fostered fundamental and meaningful peer relationships for ALHIV. Caregivers felt peer support groups increased self-acceptance and adherence for ALHIV across 3 domains: (1) as motivation for families and adolescents, (2) to increase adolescent independence and maturity, and (3) to help adolescents accept their HIV status and live successfully with HIV. These data highlight the importance of psychosocial support groups for ALHIV and caregivers, illustrating

													to treatment; (2) psychosocial support and the role of the peer groups; and (3) different aspects of conditional economic incentives, including acceptability, likely influences on behavior, and the preferred format.	the benefits of a safe space with trusted relationships and open communication.
Out-of-Facility Multimonth Dispensing of Antiretroviral Treatment: A Pooled Analysis Using Individual Patient Data From Cluster-Randomized Trials in Southern Africa	Lopes et al., 2021	Journal article	2017 and 2018	Zimbabwe and Lesotho	HIV positive patients who are on first-line ART	Study facilities (n = 60) were public health facilities in 8 high HIV-prevalence districts of Zimbabwe and Lesotho in Southern Africa.	A meta analysis using individual-level data from the 2 cluster randomized trials.	10136	**Control arm (3MF)**: Participants received facility-based standard-of care ART and clinical consultations at three-monthly intervals. **Intervention arm 1 (3MC):** Participants received ART at three-monthly intervals within community ART groups (CAGs) with annual facility visits and clinical consultations. **Intervention arm 2 (6MC):** Participants received ART at 6-monthly intervals within CAGs (Zimbabwe) or at community distribution points	Median: 3MF: 44.1 (IQR 36.4–53.8), 3MC 47,4 (IQR 40.1–57.0), 6MC 43.0 (IQR 35.2–52.6)	3MF: 66,4% female, 3MC: 72,6% female, 6MC: 69,0% female	HIV	The primary outcome was the proportion of enrolled participants retained in ART care after 12 months by intention-to-treat including participants in each arm as per baseline allocation. Secondary outcomes were the proportions achieving VS after 12 months, retention in the study arm (retention in the randomized strategy), all-cause mortality after 12 months, incidence of unscheduled facility visits between months 0–12 after enrolment and participant attrition from ART care using time-to-event analyses until 18 months in Zimbabwe (follow-up data collection did not continue to 18 months in Lesotho).	Ten thousand one hundred thirty-six participants were included, 3817 (37.7%), 2893 (28.5%) and 3426 (33.8%) in arms 3MF, 3MC and 6MC, respectively. After 12 months, retention was non-inferior for 3MC (95.7%) vs. 3MF (95.0%) {adjusted risk difference (aRD) = 0.3 [95% confidence interval (CI): −0.8 to 1.4]}; and 6MC (95.1%) vs. 3MF [aRD = −0.2 (95% CI: −1.4 to 1.0)]. Retention was greater amongst intervention arm participants in CAGs versus 6MC participants not in CAGs, aRD = 1.5% (95% CI: 0.2% to 2.9%). Viral suppression was excellent (≥98%) and unscheduled facility visits were not increased in the intervention arms.

									(Lesotho) with annual facility visits and clinical consultations.					
The Money, It's OK but It's not OK: Patients' and Providers' Perceptions of the Acceptability of Cash Incentives for HIV Treatment Initiation in Cape Town, South Africa	Swartz et al., 2021	Journal article	2015-2016	Cape Town, South Africa	HIV positive patients who are on ART	Mobile health clinic in Cape Town	Qualitative study with in-depth interviews	64	The intervention group received the standard of care plus a voucher that could be exchanged for R300 (~ $25USD) cash if ART was started within three months. After ART initiation, participants in the intervention group met with the study staff to verify ART initiation and receive the incentive.	Not specified	Not specified	HIV	No clear outcome measure documented. Data analysis adopted a combination of inductive and deductive approaches, following the specific elements of the Sekhon et al framework that guided this analysis, namely affective attitudes and ethicality. Potential links between emergent themes and the dimensions of affective attitudes and ethicality of incentives were explored. Data from the patient and provider perspectives enabled the comparisons and contrasting perspectives, thereby contributing to a richer and deeper understanding of attitudes and perceptions of incentives.	Drawing on in-depth interviews with patients and health care workers (HCWs), we find that, despite the perception that cash incentives are effective in promoting ART initiation, significant ambivalence surrounds the acceptability of such incentives. The receipt of a financial incentive was highly moralized, and fraught with challenges. Increasing the acceptability of cash incentives through careful design and delivery of interventions is central to the potential of this type of intervention for improving outcomes along the HIV care continuum.
Community-based differentiated service delivery models incorporating multi-month dispensing of antiretroviral	Fatti et al., 2021	Journal article	2017-2019	Zimbabwe and Lesotho	HIV positive patients who are on ART	Community-based differentiated service delivery	Cluster-randomized trial	599	**Control arm (SoC):** Participants received standard-of-care ART and clinical consultations at three-monthly intervals at	Median age: All participants: 39.8 (IQR 32.8–49.6); SoC: 38,6 (IQR 32.2–48.1); 3MC: 42,6 (IQR 35.7–50.7);	SoC: 55,7% female; 3MC: 75% female; 6MC:64,5 % female	HIV	The primary outcome was the proportion remaining in ART care 12 months after enrolment by intention-to-treat including participants in each arm as per baseline allocation. Secondary outcomes	A total of 599 participants were included; 212 (35.4%), 128 (21.4%) and 259 (43.2%) in SoC, 3MC and 6MC, respectively. Few participants aged <25 years were included (n = 32). After 12 months, 198 (93.4%), 123 (96.1%) and 248 (95.8%) were retained in SoC, 3MC and 6MC, respectively. Retention in 3MC was superior versus SoC, adjusted risk

treatment for newly stable people living with HIV receiving single annual clinical visits: a pooled analysis of two cluster-randomized trials in southern Africa									facilities. **Intervention arm 1 (3MC):** Participants received ART at three-monthly intervals in community ART groups (CAGs) with annual facility visits and clinical consultations. **Intervention arm 2 (6MC):** Participants received ART at six-monthly intervals in CAGs (Zimbabwe) or community distribution points (Lesotho) with annual facility visits and clinical consultations.	6MC: 39,8 (IQR 32.1–49.6)			were proportions achieving viral suppression (VS) after 12 months, and the number of unscheduled facility visits between months 0 and 12.	difference (aRD) = 4.6% (95% CI: 0.7%−8.5%). Retention in 6MC was non-inferior versus SoC, aRD = 1.7% (95% CI: −2.5%−5.9%) (prespecified non-inferiority aRD margin −3.25%). VS was similar between arms, 99.3, 98.6 and 98.1% in SoC, 3MC and 6MC, respectively. Adjusted risk ratio's for VS were 0.98 (95% CI: 0.92−1.03) for 3MC versus SoC, and 0.98 (CI: 0.95−1.00) for 6MC versus SoC. Unscheduled clinic visits were not increased in intervention arms: incidence rate ratio = 0.53 (CI: 0.16−1.80) for 3MC versus SoC; and 0.82 (CI: 0.25−2.79) for 6MC versus SoC.
Pharmacist-led medication therapy management of diabetes club patients at a primary healthcare clinic in Cape Town, South Africa: A retrospective and prospective audit	Sonday et al., 2022	Journal article	2016 and 2017	Cape Town, South Africa	Type 2 diabetes mellitus patients	Community day centre (CDC)	Evaluation study design using a case study approach	104	Medication Therapy Management (MTM) intervention among stable diabetes club patients. The CDC has a functional 'club' system whereby patients with DM who adhere to their medicine	57,7 (SD±9.2), range: 26-80	Female (67.3%)	DM	An evaluation of the implementation of a pharmacist-led MTM intervention to optimise the management of stable patients with type 2 DM attending a diabetes club at a Cape Town community day centre.	Of 104 patient folders audited, most were for females (n=70; 67.3%). A total of 453 MTPs were identified, averaging four interventions per folder reviewed. The most common MTPs identified were the absence of basic clinical data: body mass index not documented (22.5%) in the folder, no medical indication noted (19.2%), and laboratory tests not requested (18.3%) by clinicians. Prescriber acceptance of the pharmacist's recommendations was found to be low (26.8%), suggestive of clinical inertia. Aspirin was found

									regimen and have minimal changes in their clinical status (classified as stable) are referred to the club, to which they return every 6 months for their follow-up appointment. 'Stable' diabetes club patients are seen by either the club doctor or a clinical nurse practitioner (CNP) and their appointment dates are recorded in a club register.					to be irrationally prescribed to patients with DM (15.4%).
The role of pharmacy personnel in promoting adherence to antiretroviral therapy in the Eastern Cape: communication barriers and breakthroughs	Rattine-Flaherty et al., 2021	Journal article	2018	Eastern cape, South Africa	Pharmacy personnel	Public health clinics	Qualitative study with in-depth interviews	24	Pharmacy support	Age not specified	Not specified	HIV	No clear outcome measure documented. An understanding of what role pharmacy personnel believe that they play in the goal of patient adherence: an exploration of the key communication challenges faced by pharmacy staff as they serve patients with HIV and the strategies these health providers use to address personal, cultural and environmental barriers that impede effective	Pharmacy personnel identified three key sets of communication challenges that limited effective patient counselling on antiretroviral therapy. These included environmental barriers presented by clinic design, language barriers between patients and pharmacy personnel, and varying communication styles and education levels of pharmacy staff and patients. Additionally, pharmacy personnel described innovative strategies they use to improve patient-provider communication and address adherence issues.

													patient counselling and limit adherence.	
One Pill, Once a Day: Simplified Treatment Regimens and Retention in HIV Care	Bor et al., 2022	Journal article	2011 to 2014	Themba Lethu clinic, Johannesburg, South Africa	HIV positive naive adult patients initiating first-line ART	ART treatment clinic	Quasi experimental regression discontinuity design	4484	Fixed-dose combinations (FDCs) combining 3 antiretroviral medications into a single daily pill.	38,5 (SD±9.9)	Male (43%)	HIV	Our primary exposure was whether the patient starting ART was prescribed an FDC or multiple-pill regimen ("regimen type"). We classified patients as starting FDC if either source indicated an FDC regimen. We assumed that patients who initiated ART prior to the September 2012 availability of pharmacy data were prescribed multiple pills, since FDCs were not yet available. We used date of ART initiation as the assignment variable in the RDD, with patients starting on April 1, 2013, or later exposed to the new guidelines.	The share of patients prescribed a single-pill regimen increased by over 40 percentage points between March and April 2013. Initiating treatment after the policy change was associated with 11.7–percentage-points' higher retention at 12 months (95% confidence interval: −2.2, 29.4). Findings were robust to different measures of retention, different bandwidths, and different statistical models. Patients starting treatment early in HIV infection—a key population in the test-and-treat era—experienced the greatest improvements in retention from single-pill regimens.
Intervention development of a brief messaging intervention for a randomised controlled trial to improve diabetes treatment adherence in sub-Saharan Africa	Leon et al., 2021	Journal article	2018	Lilongwe, Milawi and Cape Town, and Johannesburg South africa	Type 2 diabetes mellitus patients	Public sector health facilities in urban/ peri urban sites	Randomized controlled trial with multiple, qualitative research strategies.		SMS text Adherence support for people with type 2 diabetes (StarR2D). The aim of the StAR2D intervention development study was to ensure the final brief (SMS) text-message intervention was theory- and	Lilongwe, Malawi: age range 28–78 years), Cape Town, South Africa, age range 47–80 years) (Johannesburg, South Africa, age 42–68 years)	Not specified	DM	The primary focus of this paper is to document a systematic, transparent approach to intervention development in the context of an intervention that was tested experimentally. A secondary, but important focus is on the evidence generated in each phase to illustrate its	We used a four-phase, iterative approach that first generated primary and secondary evidence on the lived experience of diabetes, diabetes treatment services and mobile-phone use. Second, we designed a type 2 diabetes-specific, brief text-message library, building on our previous hypertension text-message library, as well as drawing on the primary and secondary data from phase one, and on expert opinion. We then mapped the brief text-messages onto behaviour change (COM-B) theoretical constructs. Third, we refined and

									evidence-informed, relevant, and acceptable to the target audiences, and appropriately aligned with the organisation of clinic care at the trial sites. Intervention messages were meant to advise people about the benefits of their diabetes treatment and offer motivation and encouragement around lifestyle and use of medication.				contribution to shaping the final intervention.	finalised the newly developed brief text-message library through stakeholder consultation and translated it into three local languages. Finally, we piloted the intervention by pre-testing the automated delivery of the brief text-messages in the trial sites in Malawi and South Africa. The final SMS text Adherence support for people with type 2 diabetes (StAR2D) intervention was tested in a randomised controlled trial in Malawi and South Africa

Multimonth dispensing of up to 6 months of antiretroviral therapy in Malawi and Zambia (INTERVAL): a cluster-randomised, non-blinded, non-inferiority trial	Hoffman et al., 2021	Journal article	2017 and 2018	Malawi and Zambia	HIV positive adult patients who are on ART	30 public health faclities	A pragmatic, cluster-randomised, unblinded, non-inferiority trial	9118	Matched clusters were randomly assigned (1:1:1) to receive standard of care ART dispensing (ART typically given every 1–3 months, depending on provider judgment), 3-monthly (ie, 90-day) ART dispensing, or 6-monthly (ie, 180-day) ART dispensing. For all groups, clinical service delivery occurred simultaneously with the dispensing visits. Thus, the only differences between the study groups were the frequency of clinical consultations and the amount of ART given at these visits.	42·7 years (IQR 36.1–49·9)	Female (66.2%)	HIV	The primary outcome was retention in care at 12 months, defined as the proportion of patients with less than 60 consecutive days without ART during study follow-up, analysed by intention to treat. Secondary outcomes were viral suppression (defined as <1000 copies per mL in Malawi and <20 copies per mL in Zambia), feasibility and acceptability of dispensing intervals to participants and providers, and cost (per patient achieving the primary outcome in each group).	Between May 15, 2017, and April 30, 2018, 9118 participants were randomly assigned, of whom 8719 participants (n=3012, standard of care group; n=2726, 3-monthly ART dispensing group; n=2981, 6-monthly ART dispensing group) had primary outcome data available at 12 months and were included in the primary analysis. The median age of participants was 42·7 years (IQR 36·1–49·9) and 5774 (66·2%) of 8719 were women. The primary outcome was met by 2478 (82·3%) of 3012 participants in the standard of care group, 2356 (86·4%) of 2726 participants in the 3-monthly ART dispensing group, and 2729 (91·5%) of 2981 participants in the 6-monthly ART dispensing group. After adjusting for clustering, for retention in care at 12 months, the 6-monthly ART dispensing group was non-inferior to the standard of care group (percentage-point increase 9·1 [95% CI 0·9–17·2]) and to the 3-monthly ART dispensing group (5·0% [1·0–9·1]).

A nurse-led intervention to improve management of virological failure in public sector HIV clinics in Durban, South Africa: A pre- and post-implementation evaluation	Sunpath et al., 2021	Journal article	2017	Durban, South Africa	HIV positive adult patients who are on first-line ART	3 public health HIV clinics	Controlled before-after observational design	116	A health system-strengthening programme to manage VF at each of the three clinics. The programme included the following elements: Assignment of a nurse as the 'VL champion' at each clinic to supervise the staff responsible for monitoring all patients with a detectable VL and Development of an SOP for management of VF by clinic staff. Training on the SOP was provided to: (i) a lay counsellor or nurse assigned to adherence counselling; (ii) a nurse and/or doctor assigned to manage the VF clinic; (iii) an administrative clerk for records handling; and (iv) a data clerk to ensure same-day data	Pre-intervention: 36 (IQR 23–41), post-intervention: 35 (IQR 30 – 39)	Pre-intervention: 35% female and post-intervention: 25% female	HIV	The primary outcome was appropriate response completed to the repeat VL, specifically a VL <1 000 copies/mL or change to a protease inhibitor-based regimen after a repeat VL >1 000 copies/mL within 6 months of VF. Secondary outcomes included completion of at least one EAC session and completion of a repeat VL within 6 months.	We identified 60 and 56 individuals in the pre-intervention and post-intervention periods, respectively, with VF who met the inclusion criteria. Sociodemographic and clinical characteristics were similar between the periods. Repeat VL testing was completed in 61.7% and 57.8% of individuals in these two groups, respectively. We found no difference in the proportion achieving our primary outcome in the pre- and post-intervention periods: 11/60 (18.3%; 95% confidence interval (CI) 9 - 28) and 15/56 (22.8%; 95% CI 15 - 38), respectively (p=0.28). In multivariable logistic regression models adjusted for potential confounding factors, individuals in the post-intervention period had a non-significant doubling of the odds of achieving the primary outcome (adjusted odds ratio 2.07; 95% CI 0.75 - 5.72). However, there was no difference in the rates of completion of each step along the first-line VF cascade of care.

									entry. In brief, VL results were reviewed daily by the VL champion and filed or entered in the patient charts. The lay counsellor also managed completion of the high VL register and was expected to call patients who missed a clinic appointment within a week at any point of the follow-up period.					
Impact of SMS and peer navigation on retention in HIV care among adults in South Africa: results of a three-arm cluster randomized controlled trial	Steward et al., 2021	Journal article	2014 and 2015	North West Province, South Africa	HIV positive adult patients who are on ART	Clinical sites included five community healht centres and 13 primary health clinics.	Three-arm cluster randomized controlled trial	752	1. **The SMS-only intervention** used an automated messaging system to deliver three kinds of SMS. First, reminders were sent prior to clinic appointments, and every two weeks after missed appointments until a participant returned to care or three months elapsed. Second, brief	Just over half were younger than 35	SoC: 61,2% Female; SMS-only: 58,1% Female; SMS+PN: 64,2% Female	HIV	The trial outcome, retention in care, was measured at the individual level and defined by ART status.	Between October 2014 and April 2015, we enrolled 752 adult clients recently diagnosed with HIV (SOC: 167; SMS-only: 289; SMS+PN: 296). Individuals in the SMS+PN arm had approximately two more clinic visits over a year than those in other arms ($p < 0.01$) and were more likely to be retained in care over one year than those in SOC clinics (54% vs. 38%; OR: 1.77, CI: 1.02, 3.10). Differences between SMS+PN and SOC conditions remained significant when restricting analyses to the 628 participants on ART (61% vs. 45% retained; OR: 1.78, CI: 1.08, 2.93). The SMS-only intervention did not improve retention relative to SOC (40% vs. 38%, OR: 1.12, CI: 0.63, 1.98).

									behavioural messages were sent biweekly to encourage engagement in care, adherence, prevention (e.g. disclosure to sexual partners) and healthy living (e.g. reduced alcohol use). Third, SMS check-in messages were sent biweekly, asking participants to reply, free of charge using a numeric code, to indicate if they were experiencing challenges. 2. **The SMS+PN intervention** used the same automated system to send SMS appointment reminders and biweekly behavioural messages. Additional support was provided by peer navigators, who were PLHIV receiving care at a local					

								facility. Navigators met each client in-person at least once per month and had one phone or SMS check-in mid-month. 3. **Participants at SOC clinics** (Standard of Care) did not receive services beyond standard care. P					
Diabetes self-management: a qualitative study on challenges and solutions from the perspective of South African patients and health care providers	Masupe et al., 2022	Journal article	2018	Cape Town, South Africa	Type 2 melltus diabetes and/or hypertensive patients	2 community health centres	Qualitative study with 8 in-depth interviews and 4 mixed focus groups.	43	Self-management support. Self-management is described based on tasks that fall within three categories: medical/behavioural management, role management, and emotional management. The medical/behavioural role entails proper use of medication for disease control and adopting positive health behaviours geared towards slowing down	Age range was 38–75 years	8 Males and 35 Females	HTN AND DM	Identify self-management barriers, and solicit solutions for enhancing self-management of T2D/HTN from patients and their healthcare providers	Patients experienced challenges across all three self-management tasks of behavioural/medical management, role management, and emotional management. Main challenges included poor patient self-control towards lifestyle modification, sub-optimal patient-provider and family partnerships, and post-diagnosis grief-reactions by patients. Barriers experienced were stigma, socio-economic and cultural influences, provider-patient communication gaps, disconnect between facility-based services and patients' lived experiences, and inadequate community care services. Patients suggested empowering community-based solutions to strengthen their disease self-management, including dedicated multidisciplinary diabetes services, counselling services; strengthened family support; patient buddies; patient-led community projects, and advocacy. Providers suggested contextualised communication using audio-visual

								disease progression. Role management defines new long-term partnerships between patients and healthcare professionals where the patient plays a role of a partner, accurately and truthfully reporting any changes in symptoms. The emotional role consists of the patient's emotional reactions to chronic disease.					technologies and patient-centred provider consultations.
Impact of Friendship Bench problem-solving therapy on adherence to ART in young people living with HIV in Zimbabwe: A qualitative study",2021	Ouansafi et al., 2021	Journal article	2019	Harare, zimbabwe	Young people (aged 18-24 years) living with HIV	Primary care clinics	Qualitative study	10	The friendship Bench (FB)-an innovative model developed in Zimbabwe to bridge the gap in mental health treatment. Embedded within the City Health Department of Harare, it offers problem-solving therapy delivered on benches in	Age range: 18-24 years	Female (70%)	HIV	Exploration of the experiences of young people living with HIV attending FB, and their perception of how problem-solving therapy impacted their adherence to ART.	Study findings revealed a clear emotional denial towards HIV, particularly for young people infected perinatally, and a resulting low adherence to ART. The study also unpacked the issues of internal stigma and how young people living with perinatally acquired HIV are informed of their HIV status. Participants reported that FB had a critical role in helping them accept their HIV status. Grandmothers' empathic attitude was key during counselling on adherence to ART, to demystify the disease and treatment, normalize the reality of living with HIV, encourage young people to socialize with peers and free them of guilt. Interviewees

									primary care facilities by trained lay health workers (LHWs), elderly women commonly known as community "grandmothers". FB counselling consists of six sessions generally completed within four to six weeks. LHWs ask questions, encourage clients to "open their minds", identify a problem and proactively tackle it. Following problem identification and exploration, LHWs guide their clients on an action plan towards a feasible solution.					unanimously reported improved ART adherence following FB counselling, and many described enhanced health and wellbeing.

Group medical visit and microfinance intervention for patients with diabetes or hypertension in Kenya	Vedanthan et al., 2021	Journal article	Not specified	Kenya	Mellitus Diabetes or Hypertension patients	Health care facility	Cluster randomized trial	2890	**In the UC arm,** participants received AMPATH's multicomponent chronic disease management care package. The clinical protocol aligned with contemporaneous relevant global and national guidelines, using drugs contained in the Kenyan national formulary, and included both pharmacologic and nonpharmacologic interventions. There was no charge for the clinical encounter. Standard fees for medications were negotiated between AMPATH and the Kenyan Ministry of Health and did not vary across the trial arms, so that price differences	60.7 (SD±12.1)	Female: 2020 (69.9%)	HTN AND DM	The primary outcome measure was 1-year absolute mean change in SBP, measured by trained study staff using electronic BP machines and standardized procedures. Key secondary outcome measures included change in DBP and change in 10-year CVD event risk as measured by the QResearch-based QRISK3 score. Other secondary outcomes included BP control (SBP<140 mm Hg and DBP<90 mm Hg), change in total and low-density lipoprotein cholesterol, change in the International Wealth Index (asset-based index of a household's material well-being, used in LMICs), and change in livestock ownership.	A total of 2,890 individuals (69.9% women) were enrolled (708 UC, 709 MF, 740 GMV, and 733 GMV-MF). Average baseline SBP was 157.5 mm Hg. Mean SBP declined11.4,14.8,14.7, and16.4 mm Hg in UC, MF, GMV, and GMV-MF, respectively. Adjusted estimates and multiplicity-adjusted 98.3% confidence intervals showed that, relative to UC, SBP reduction was 3.9 mm Hg (8.5 to 0.7), 3.3 mm Hg (7.8 to 1.2), and 2.3 mm Hg (7.0 to 2.4) greater in GMV-MF, GMV, and MF, respectively. GMV and GMV-MF tended to benefit women, and MF and GMV-MF tended to benefit poorer individuals. Active participation in GMV-MF was associated with greater benefit.

									would not bias study results. At the time of the study, the Kenyan national health insurance plan did not cover outpatient chronic disease medications. **In the MF arm,** participants received usual multicomponent clinical care and were encouraged to create MF groups that met monthly and were organized and supported by AMPATH. AMPATH's MF program involves the creation of community savings groups, wherein MF group members mobilize and manage their own savings, provide interest-bearing loans to group members, offer a limited form of financial insurance, and contribute to a social fund used for emergency					

									or welfare issues of group members. No external funds are provided to the MF groups. All MF group participants received loans from the combined group savings. **In the GMV arm,** participants were invited to join a group that met monthly with a community health worker and clinician (either physician or clinical officer) at a location convenient to the community health worker, clinician, and participants. The clinical care package was identical to the multicomponen t AMPATH chronic disease management package, but the delivery was in the form of a GMV rather than individual clinician-patient					

									encounter in the health facility. Each GMV began with the measurement of resting BP (all participants) and blood glucose (diabetes patients), the ascertainment of medication regimen for each participant, and extent of medication adherence. Subsequently, the community health worker facilitated a group discussion about a self-care or health education topic chosen by the group. The community health worker had received training in motivational interviewing, chronic disease self-management techniques, and group-based peer support, and					

									encouraged group members to engage in mutual problem solving and sharing of ideas. During this time, the clinician reviewed the BP, glucose, and adherence data to determine a clinical management plan for each individual. After the group discussion ended, each participant had a brief individual consultation with the clinician during which their individual management plan was discussed and finalized. Each GMV lasted for 2h. **In the GMV-MF arm**, the monthly GMV was integrated into the MF groups, wherein each group meeting consisted of an initial MF portion,					

								followed by the GMV. Thus, participants received their clinical care in a GMV as well as participated in MF, as described above.					
Social support for self-care: patient strategies for managing diabetes and hypertension in rural Uganda	Tusubira et al., 2021	Journal article	2019	Nakaseke, Uganda	Mellitus Diabetes and/or Hypertension patients	NCD clinics at three health facilities in rural Uganda	Cross-sectional qualitative study	19	Self-care practices and social support: Self-care is a patient-driven process involving activities intended to manage symptoms and maintain physiological stability. Self-care includes all actions patients take to attain and maintain good health. Social support may take the form of physical, financial, or psychological help from family, friends, and community members. It may consist	55 (SD±12)	Female (47%)	HTN AND DM	An exploration of practices and resources for attaining and maintaining health in light of diagnosis with diabetes and/or hypertension.	Nineteen patients participated. Patients said they preferred conventional medicines as their first resort, but often used traditional medicines to mitigate the impact of inconsistent access to prescribed medicines or as a supplement to those medicines. Patients adopted a wide range of vernacular practices to supplement treatment or replace unavailable diagnostic tests, such as tasting urine to gauge blood-sugar level. Finally, patients sought and received both instrumental and emotional support for self-care activities from networks of family and peers. Patients saw their children as their most reliable source of support facilitating self-care, especially as a source of money for medicines, transport and home necessities.

								either of emotional support (i.e., a confidant) or instrumental support (i.e., tangible and/or physical assistance).					
Adherence to diabetes self-care management and associated factors among people with diabetes in Gamo Gofa Zone public health hospitals	Agidew et al., 2021	Journal article	2018	Gamo Gofa Zone, Southern Ethiopia	Mellitus Diabetes patients	6 Public health hospitals	Institutional -based quantitative cross sectional study	635	These hospitals have been giving preventive, curative and rehabilitative service for the catchment population including diabetes and other chronic none communicable diseases.	48,47 (SD±13.86)	Female (49.5%)	DM	Adherence to diabetes self-care management was the dependent variable while socio-demographic characteristics, dietary feeding practice, physical exercise, eye examination practice and foot care practices were some of the independent study variables as indicated in the result section.	The prevalence of good adherence toward diabetes self-care management was 341 (53.7%), (95% confidence interval=46.09, 61.31). Regarding diabetes self-care practices, poor adherence had been detected in blood sugar measurement practice, dietary feeding practice, physical exercise and eye examination practice. The multivariable analysis indicated that government workers [adjusted odds ratio=2.74 (1.03, 7.30)], training on diabetes self-care practice [adjusted odds ratio=3.13 (1.89, 5.16)], diabetes' association membership [adjusted odds ratio=1.59 (1.01, 2.50)], having personal glucometer at home [adjusted odds ratio=2.70 (1.37, 5.33)], duration of diabetic illness >10 years [adjusted odds ratio=9.59 (3.99, 23.05)] and people with diabetes who were not developing complication [adjusted odds ratio=1.54 (1.01, 2.33)] were significantly associated with good adherence to diabetes self-care management practice.

Family support and medication adherence among adult type 2 diabetes: Any meeting point?	Olagbemide et al., 2021	Journal article	2016	Ido-Ekiti, Nigeria	Type 2 Mellitus Diabetes patients	Department of family medicine at a federal teaching hospital. A tertiary healthcare facility	Cross-sectional hospital-based study	367	Self-care practices and social support: Self-care is a patient-driven process involving activities intended to manage symptoms and maintain physiological stability. Self-care includes all actions patients take to attain and maintain good health. Social support may take the form of physical, financial, or psychological help from family, friends, and community members. It may consist either of emotional support (i.e., a confidant) or instrumental support (i.e., tangible and/or physical assistance).	61,7 (SD± 11.4)	Female (51.4%)	DM	The relationship between family support and medication adherence among adult Type 2 DM (T2DM) attending family medicine clinic of a rural tertiary hospital.	The mean (standard deviation) age of respondents was 61.7 ± 11.4 years. Those with strong family support that achieved medium/high (Morisky Medication Adherence Scale-8 > 6) level of medication adherence (odds ratio [OR] [95% confidence interval (CI)] = 1 6.4 [9.1–29.6], P < 0.001) constituted 69.5% of respondents. Family support was also found to have a direct relationship to glycemic control (FPG < 7.1 mmol/l), 65.7% of those with strong family support achieved good glycemic control, P < 0.001, OR (95% CI) = 17.4 (9.2–37.2). The level of medication adherence was noted to be directly related to glycemic control, 79.4% of those with medium/high medication adherence had good glycemic control, OR (95% CI) = 25.0 (14.4–43.6), P < 0.001. Strong family support leads to higher medication adherence level which resulted into better glycemic control.

EFFECT OF HEALTH EDUCATION INTERVENTION IN THE MANAGEMENT OF TYPE-II DIABETES MELLITUS AMONG ADULTS ATTENDING GARISSA COUNTY REFERRAL HOSPITAL, KENYA	Abdalla, 2022	Thesis	Not specified	Kenya	Type 2 Mellitus Diabetes patients	Garissa county referral Hospital	Quasi experimental study	152	The intervention group (treatment arm or cases) received a health education package on DM2 comprising education on the disease in terms of causes and risk factors, clinical presentation and complications, screening and diagnosis, management, and control of the disease adapted from the American Diabetes Association. Both the cases (intervention or treatment arm) and the controls received standard diabetic care comprising of medical, nutritional, physical, and counselling care. This standard of care has been shown to	Cases (median, 46.0; range, 18.0-84.0 years) and controls (median, 42.0; range, 18.0-81.0 years)	Female: 55,4% intervention group and 34,8 % control group	DM	The effect of group health education.	Socio-demographic and socio-economic assessment indicated that the distribution of age, gender, education levels, marital status, monthly house-hold income, house-hold size, and familial history of diabetes was similar between the cases and controls. The prevalence of type-2 diabetes was 16.6%. Lifestyle evaluation indicated higher rates of smoking a pack of cigarettes daily (71.1% vs. 24.6%) or more than a pack of cigarettes daily (9.6% vs. 17.4%; χ 2 =33.289; df=2; P<0.0001) in the cases and controls, respectively. Overall levels of good knowledge in the cases and controls at baseline (57.8% vs. 72.5%; χ2 =3.816; df=1; P=0.051); and after intervention (88.0% vs. 66.7%; χ2 =11.058; df=1; P=0.001), respectively. Diabetic control marker analysis indicated that only HbA1c levels were significantly lower in the cases compared to controls at baseline (P=0.002). After intervention, BMI (P=0.005), HbA1c (P<0.0001) and fasting glucose (P<0.0001) were significantly lower in the cases relative to the controls. In addition, among the intervention group, the BMI, HbA1c, LDL-cholesterol, HDL-cholesterol, triglycerides and fasting glucose were significantly lower after intervention compared to baseline levels (P<0.01 for all).

									improve treatment outcomes, lower the chances of developing complications among DM2 patients, and risk of developing diabetes among prediabetics. The intervention group attended a education program that lasted 6 hours, twice a week for each session, i.e., baseline, and end-term for three weeks over the 6-month study period. The education intervention was facilitated by the principal investigator, and a public health officer research assistant. The educational techniques used in this study included brainstorming, question and answers,					

									scenarios, and group discussion. At baseline and at 6-months after intervention (end-term); physical measurements (height and weight measurements were performed and BMI calculated), and serum samples were collected for analysis of the clinical laboratory markers of diabetes (glucose, glycated haemoglobin, and lipid profile).					
Adherence to Diabetes Self-Management and Its Associated Factors Among Adolescents Living with Type 1 Diabetes at Public Hospitals in Addis Ababa, Ethiopia: A Cross-	Geneti et al., 2022	journal article	2022	Addis ababa, Ethiopia	Type 1 Mellitus Diabetes adolescents	Diabetic clinic at public hospitals	Institutional -based quantitative cross sectional study	422	Diabetes Self-management: Refers to behaviours such as following adherence to the management of insulin administration, dietary management, management of hypoglycemia, blood glucose	Mean age of 13.64 years (range: 10-18 years)	Female (56.5%)	DM	Adherence to diabetes self-management (ADSM): Data about self-management activities was collected using the tool called "Validation of a self-report version of the diabetes self-management profile" which was cross-culturally adapted in Hindi in 2020. Its reported internal consistency reliability was α=0.835. This	In this study, a total of 414 diabetic adolescents were interviewed making a 98.1% response rate. About 218 participants (52.7%) had poor adherence to overall diabetes self-management. Self-efficacy (AOR=8.7, 95% CI:1.9-14.1, P=0.005), social support (AOR=4.6, 95%CI:1.5-13.5, P=0.006), age (AOR=0.2, 95%CI:0.1-0.4, P=0.001), good knowledge of the disease (AOR=9.046, 95%CI:3.83-13.5, P=0.000), moderate knowledge (AOR=6.763, 95%CI:2.18-12.921, P=0.001), and time since diagnosis of type 1 diabetes (AOR=0.1,

Sectional Study									testing, and regulation of exercise. The percentage was calculated and categorized as good adherence to diabetes self-management if 'diabetes self-management profile self-report questionnaire' scores >50% and poor adherence to diabetes self-management for scores <50%				Diabetes Self-Management Profile Self-Report (DSMP-SR) has 24 item instrument that quantifies five areas of diabetes self-management which were insulin administration (4 items), dietary management (6 items), hypoglycemia management (4 items), blood glucose testing (7 items), and exercise (3 items). Then 5-point Likert scale with the anchors 1=never, anchors 2=Almost never, anchors 3=Sometimes, anchors 4=Almost always, anchors 5=always was used. Therefore, those with scores greater than 50% are categorized as having good adherence and those with scores less than or equal to 50% are categorized as having poor adherence.	95%CI:0.02-0.2, P=0.005) were significantly associated with adherence to diabetes self-management.

HIV-and hypertension-related knowledge and medication adherence in HIV seropositive persons with hypertension	Jackson et al., 2022	Journal article	Not specified	Cross River State, Nigeria	Hypertensive patients who HIV seropositive	University of Calabar Teaching Hospital, HIV clinic.	Descriptive, cross-sectional study	199	Intervention: HIV- and hypertension-related knowledge	46 (IQR 38–58) years	Female (57.3%)	HIV AND HTN	Hypertension-related knowledge compared to HIV-related knowledge and a comparison between ART adherence and antihypertensives adherence.	Participants were predominantly females (57.3%), with a median (IQR) age of 46 (38–58) years; majority were married (67.8%) and employed (60.8%). Participants reported a higher hypertension-related knowledge compared with HIV-related knowledge (63.6% versus 33.3%, Z = −10.263, P < 0.001), but better adherence to antiretroviral medications compared to antihypertensives (100.0% versus 89.3%, Z = −9.118, P < 0.001). Of the 98 participants with documented viral load, 55 (56.1%) had undetectable (<40 copies/ml) values; however, only four (2.0%) of the entire sample had controlled (<140/90 mmHg) blood pressure.
Family support and medication adherence among residents with hypertension in informal settlements of Nairobi, Kenya: a mixed-method study	Xiong et al., 2022	Abstract	Not specified	Nairobi, Kenya	Hypertensive patients	Two health facilities in informal settlement areas of the Korogocho neighborhood	Mixed-method study	93	Family support	Mean age: 57(SD±14.7)	Female (66%)	HTN	exploration of the relationship between family support and medication adherence among people with hypertension	A total of 93 people participated in the survey (mean age: 57 ± 14.7, 66% female). Most participants reported high family support (82%, n = 76) and suboptimal medication adherence (43% by the Morisky Scale; 76% by the Hill-Bone Scale), with no significant associations between family support and medication adherence. During interviews, many participants reported they lacked health knowledge and education. We suggest that the lack of health knowledge among this population may have contributed to a failure for family support to meaningfully translate into improvements in medication adherence.

PEERNaija: A Gamified mHealth Behavioral Intervention to Improve Adherence to Antiretroviral Treatment Among Adolescents and Young Adults in Nigeria	Ahonkhai et al., 2021	Journal article	Not specified	Nigeria	Adolescents and young adults living with HIV (AYA-HIV) who have poor adherence to ART	Nigerian Institute of Medical Research	Mixed method study approach	20	PEERNaija smartphone application: Key features of the guiding application include medication reminders and adherence tracking, refill and appointment reminders, leaderboard and adherence points, internal community supports through discussion forums, peer-to-peer kudos, and community-based resources list.	Age not specified	Not specified	HIV	A peer-based mHealth ART adherence intervention > PEERNaija.	PEERNaija was developed as a gamified Android-based mHealth application to support the behavioral change goal of improving ART adherence among AYA-HIV within Nigeria, a low- and middle-income country (LMIC). Identified via foundational interviews with the target population and review of the literature, key individual (forgetfulness and poor executive functioning), environmental (poor social support) and structural (indirect cost of clinic-based interventions) barriers to ART adherence for AYA-HIV informed application features. Further informed by established behavioral theories and principles, the intervention aimed to improve self-efficacy and self-regulation of AYA-HIV, leverage peer relationships among AYA to incentivize medication adherence (via contingency management, social accountability), provide peer social support through an app-based chat group, and allow for outreach of the provider team through the incorporation of a provider application. Gamification mechanics incorporated within PEERNaija include: points, progress bar, leaderboard with levels, achievements, badges, avatars and targeted behavior change messages. PEERNaija was designed as a tethered mobile personal health record application, sharing data to the widely deployed Open MRS electronic health record application. It also uses the secure opensource Nakama gamification platform, in line with Principles of Digital Development that emphasize

														use of opensource systems within LMICs.

The transient effect of a peer support intervention to improve adherence among adolescents and young adults failing antiretroviral therapy in Harare, Zimbabwe: A randomized control trial	Ndhlovu et al., 2021	Journal article	2016-2018	Zimbabwe	HIV positive adolescents and young adults on ART with virologic failure (VF)	Parirenyatwa Hospital Family Care Clinic-one of the largest referral hospitals in Zimbabwe	Randomized control trial	212	Participants enrolled in the intervention arm received SOC as practiced at the PHFCC as well as 'Zvandiri' as the intervention. "Zvandiri" is a peer-led model of layered psychosocial support services, delivered through home visits, support groups, clinic visits and mobile health, together with support for caregivers. On enrolment in the study, each participant was referred by the clinic to Africaid's Zvandiri programme and assigned to a Community Adolescent Treatment Supporter (CATS) living within their own community. CATS are young people (18–24 years old) living	18.1 (IQR: 15.1–20.0) years	Female (49.5%)	HIV	The primary outcome of this trial was the proportion of participants who were virologically suppressed (defined as HIV VL of <1000 copies/mL as per WHO guidelines adopted nationally and being used at that time) in the intervention group compared to SOC at week 36 [25].	The participants' median (interquartile range (IQR)) age was 18.1 (IQR: 15.1–20.0) years and half (50.5%, n = 107) were male. At week 24, the proportion of subjects with a detectable viremia was significantly lower in the intervention arm than in the standard of care (SOC) arm (76.0% (n = 79) vs. 89.0% (n = 96), p = 0.013). At Week 36, there remained a difference in the proportion of subjects with a detectable VL between the intervention arm (68.3%, n = 71) and SOC arm (79.6%, n = 86), which was trending towards statistical significance (p = 0.059). There was no difference in the probability of having a detectable VL over time between the intervention and SOC groups (adjusted odds ratio: 1.14, p = 0.439). Baseline HIVDR was observed in 44.0% of the participants in the intervention and 56.0% in the SOC group (p = 0.146).

									with HIV who are recruited, trained, and mentored as peer counsellors. CATS conducted weekly home visits for participants who had consented to be visited, during which they provided information, counselling, adherence monitoring and support. Each CATS delivered weekly WhatsApp messages to their designated participant. The messages provided adherence and clinic reminders and enquired about the participant's well-being.					

Social networks and barriers to ART adherence among young adults (18–24 years) living with HIV at selected primary health facilities of South-Western Uganda: A qualitative study	Ajuna et al., 2021	journal article	2020	Southwestern Uganda	Young adults living with HIV (YALWH)	2 Public primary health care facilities: 1 urban and 1 rural	Descriptive qualitative study	23	Social networks: Social networks were categorized into three namely: bonding, bridging, and linking networks. Bonding networks were defined as those that involved "strong bonds or intimate relationships with people of the same background" that supported YALWH, such as family members, spouses, friends, and neighbours. Bonding networks were indicated by individuals who were in close contact with the YALWH with whom they engaged in regular visits, talks, collaborative activities; considered confidants for HIV status disclosure and	Range: 18-24 years	Not specified	HIV	A description of the social networks of YALWH, their barriers to ART adherence, and the perceived role of social networks in overcoming barriers to ART adherence.	Most YALWH belonged to bonding (family, friends, and neighbours), followed by bridging (informal groups), and linking (health professionals) social networks, respectively. Most YALWH, irrespective of gender, had close connections with their mothers or elder sisters. The commonest form of bridging networks was informal community groups that provided financial services, whereas the linking ones comprised health professionals' directly involved in HIV patient care such as nurses, counsellors, and their affiliates (expert clients or clinic based peer supporters), who occasionally acted as bonding networks. Structural barriers to ART adherence (eg, stigma) were the most cited, followed by medication- (eg, pill burden), and patient-related barriers (eg, non-disclosure of HIV status). Bonding networks were perceived to help overcome patient, medication, and structural barriers to ART adherence. Bridging networks overcame structural and medication-related barriers to ART adherence. Linking networks were perceived to help overcome some health systems and medication-related barriers to ART adherence.

									helped YALWH overcome barriers to ART adherence. Bridging networks were defined as networks that involved weaker but more cross-cutting connections with “people of diverse backgrounds” organized in either local, regional, or national level networks of community groups.					

Effectiveness of Mobile Phone Reminders in Improving Adherence and Treatment Outcomes of Patients on Art in Adamawa State, Nigeria: A Ramdomized Controlled Trail	Suru et al., 2021	journal article	2017-2018	Adamawa State, Nigeria	HIV positive adult patients who are on ART	Nigeria (Federal Medical Centre (FMC) Yola, State Specialist Hospital Yola, St Francis Hospital Jambutu in Yola, General hospital Mubi and General hospital Mayo Belwa	Randomized control clinical trial	244	Intervention group, Mobile phone reminders: In addition to standard cares the intervention group received a minimum of three (at based line, 3 and month 6) individual counselling sessions with the research assistants lasting an average of 10 minutes per encounter, weekly text message medication reminder, text message reminders 3 days before scheduled clinic appointments and phone call a day to appointment scheduled by the trained research assistants for the period of six months. The clients who did not show up for their medication refills were	37.7% within the 36 - 45 years age grouping in the intervention group and 39.3% within the 26–35 years age grouping in the control group.	Female: the intervention (64.8%) and control (63.1%) groups	HIV	Outcome is the strength of associations and relationships between the various variables and probability of statistically significant level set.	The response rates in the intervention and control groups were 99% and 96.7% at 3 months; 97.5% and 92.6% at 6 months, respectively. Individual socio-demographic characteristics were not found to be associated with adherence levels in this study. At six months follow up the proportion of the respondents who had good adherence (>95%) was higher (89.1%) and statistically significant (p= 0.001) in the intervention group compared to control group (63.1%) and (p= 0.617). A significantly higher frequency in missed clinic appointments (7.98 vs 1.68) (p=0.024) was noticed in the control group, and a statistically significant increase in the proportion of participants who reported an increase in weight (p=0.001), CD4 cells counts (p=0.001) and decrease in the presence of tuberculosis and other opportunistic infections were observed among patients in the intervention group.

								tracked by the trained research assistant.					
Educational and Psychological Issues Effectiveness of a group diabetes education programme in under-served communities in South Africa: a pragmatic cluster randomized controlled trial	Mash et al., 2014	Journal article	2010-2011	Cape town, South Africa	Type 2 Mellitus Diabetes patients	Public sector community health centres	Pragmatic clustered randomized controlled trial	1570	The intervention consisted of four 60-min sessions of group education that focused on understanding diabetes, living a healthy lifestyle, understanding the medication and avoiding complications. Although the training manual anticipated the sessions would last up to 120 min, in reality the sessions lasted up to 60	Mean age: 56.1 (SD±11.6) years	Female: 75,7% control group, 71,5 interventio n group	DM	The primary outcome measures were defined as improved diabetes self-care activities, 5% weight loss, and a 1% reduction in HbA1c level. Secondary outcomes were improved diabetes-specific self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, mean HbA1c and mean total cholesterol levels, and quality of life.	A total of 422 (59.4%) participants in the intervention group did not attend any education sessions. No significant improvement was found in any of the primary or secondary outcomes, apart from a significant reduction in mean systolic (-4.65 mmHg, 95% CI 9.18 to -0.12; P = 0.04) and diastolic blood pressure (-3.30 mmHg, 95% CI -5.35 to -1.26; P = 0.002). Process evaluation suggested that there were problems with finding suitable space for group education in these under-resourced settings, with patient attendance and with full adoption of a guiding style by the health promoters.

									min. Health promoters recruited from the district health services were trained over a total of 6 days to deliver each session within the facility, using a guiding style of communication based on motivational interviewing principles and skills. Resource materials for group activities were developed for each session and the training manual was published elsewhere 18. The resource materials were made available in English, Afrikaans and Xhosa as necessary. Health promoters discussed the practical implementation during training and each identified a suitable location at their health centre for the group					

									education prior to the intervention.					
Effect of a nutrition education programme on clinical status and dietary behaviours of adults with type 2 diabetes in a resource-limited setting in South Africa: A randomised controlled trial	Muchiri et al., 2016	Journal article	2010 - 2011	North West Province, South Africa	Type 2 Mellitus Diabetes patients	Two community health centres, moretele sub-district	Randomized control trial	82	The control group participants received education materials (pamphlet and wall/fridge poster) and continued with the usual medical care at their respective CHC. The intervention group received the same education materials and also participated in an NE programme. The NE programme consisted of three components: (i) the curriculum (eight weekly sessions, 2 to 2·5 h each;); (ii) follow-up sessions (four monthly meetings and two bi-monthly meetings each lasting 1·5 h); and (iii) vegetable	Mean age was 58·8 (SD±7·7) years	female: intervention: 87,8%; control: 85,4%	DM	The primary outcome was the change in HbA1c at 6 months. The secondary outcomes were changes in other clinical outcomes (BMI, blood pressure and blood lipids), HbA1c and dietary behaviours at 12 months.	Differences in HbA(1c) (primary outcome) were -0·64 % (P=0·15) at 6 months and -0·63 % (P=0·16) at 12 months in favour of the intervention group. Starchy-food intake was significantly lower in the intervention group, 9·3 v. 10·8 servings/d (P=0·005) at 6 months and 9·9 v. 11·9 servings/d (P=0·017) at 12 months. Median energy intake was significantly lower in the intervention group at 12 months (5988 v. 6946 kJ/d, P=0·017). No significant group differences in BMI, lipid profile, blood pressure and intakes of macronutrients, vegetables and fruits were observed.

									gardening (demonstration of sowing/transplantation of vegetables). The NE sessions were offered in five groups of six to ten participants. The groups were formed on the basis of recruitment time; therefore, the NE sessions were staggered over the study period. The first group commenced in June 2010 and the last group completed in November 2011. Participants were restricted to their clinics as they receive their medication at a particular clinic and the NE sessions were offered at participants' respective CHC. The total NE programme contact time was 26·5 h per group for the combined					

								weekly and monthly meetings.					
Short- and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial	Sarna et al., 2008	Journal article	2003-2004	Mombasa, Kenya	HIV positive patients	A provincial referral hospital (n = 167); a private, not-for-profit clinic (n = 59); and a district hospital (n = 8).	Randomized control clinical trial	234	m-DOT (24 weeks of twice weekly health center visits for nurse-observed pill ingestion, adherence support, and medication collection	Control: 37 (SD±7.8) MDOT: 37.3 (SD±8.0)	Female: control:75 %; interventio n:74%	HIV	Levels of adherence in the 2 groups was compared in the first 24 weeks to assess effectiveness of the intervention and then compared during weeks 25-48 and week 72 to detect any sustained effects on adherence. Secondary outcomes were evaluated as follows: virological suppression, increases in CD4 cell counts, and changes in weight and BMI.	During weeks 1-24, 9.1% (9/99) of m-DOT participants reported missing doses compared with 19.1% (20/105) of controls (P = 0.04) and 96.5% (517/571) of m-DOT pill-count measures were ≥95% compared with 86.1% (445/517) in controls [adjusted odds ratio = 4.4; 95% confidence interval (CI) = 2.6 to 7.5; P < 0.001. Adherence with m-DOT was 4.8 times greater (95% CI = 2.7 to 8.6; P < 0.001) with adjustment for depression and HIV-related hospitalization. In weeks 25-48, adherence with m-DOT (488/589) was similar to controls (507/630). Viral suppression at 48 weeks was 2.0 times (95% CI = 0.8 to 5.2; P = 0.13) as likely in m-DOT participants as controls. M-DOT patients had larger body mass index increases at 24 weeks (2.2 vs 1.4 kg/m3; P = 0.014). Viral suppression was more likely at week 48 (21/25 vs 13/22; P = 0.057) and week 72 (27/30 vs 15/23; P = 0.027) among depressed participants receiving m-DOT.

Supplementary material 1_PRISMA_checklist (page numbers aligned with the individual manuscript presented in chapter 7)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg 4-6/Table 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pg 5-6/Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg 6-7/Table 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Table 1
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg 6/figure 1/table 2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	n/a

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Figure 1/Table 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	n/a
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n/a
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg 6-7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg 6-7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg 7/fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	n/a
Study characteristics	17	Cite each included study and present its characteristics.	Pg 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pg 10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg 7 and pg 10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	n/a
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Table 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg 10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg 10
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg 11-14
	23b	Discuss any limitations of the evidence included in the review.	Pg 13
	23c	Discuss any limitations of the review processes used.	Pg 13
	23d	Discuss implications of the results for practice, policy, and future research.	Pg 13-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg 3 & 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg 3 & 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	n/a
Competing interests	26	Declare any competing interests of review authors.	Pg 14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg 15-16

Supplementary material 2_GRADE Risk of Bias tool/Checklist for the Quality Assessment Tool

Study limitations (Risk of Bias)

1) Was random sequence generation used (i.e. no potential for selection bias)?
- Yes
- No
- Unclear

2) Was allocation concealment used (i.e. no potential for selection bias)?
- Yes
- No
- Unclear

3) Was there blinding of participants and personnel (i.e. no potential for performance bias)?
- Yes
- No
- Unclear

4) Was there blinding of outcome assessment (i.e. no potential for detection bias)?
- Yes
- No
- Unclear

5) Was an objective outcome used?
- Yes
- No

6) Were more than 80%[4] of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?
- Yes
- No
- Unclear

7) Were data reported consistently for the outcome of interest (i.e., no potential selective reporting)?
- Yes
- No
- Unclear

8) No other biases reported? (i.e. no potential of other bias)
- Yes
- No

9) Did the trials end as scheduled (i.e not stopped early)?
- Yes
- No

Inconsistency[5]

1) Point estimates did not vary widely?
- Yes
- No

2) To what extent did confidence intervals overlap?
- Substantial overlap
  (all confidence intervals overlap at least one of the included studies point estimate)
- Some overlap
  (confidence intervals overlap but not all overlap at least one point estimate)
- No overlap

[4] 80% drop out is given as an example here a different proportion can be used depending on the context of the systematic review area

[5] Reviewers may choose to use estimates from a subgroup analysis which may explain the inconsistency but should be cautious that such a explanation of heterogeneity may be due to the play of chance

(At least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)

3) Was the direction of effect consistent?
- Yes
- No

4) What was the magnitude of statistical heterogeneity (as measured by I^2)?
- Low (e.g. I^2 <40%)
- Moderate (e.g. I^2 40-60%)
- High (e.g. I^2 >60%)

5) Was the test for heterogeneity statistically significant (p<0.1)?
- Not statistically significant
- Statistically significant

Indirectness

1) Were the populations in included studies applicable to the decision context?
- Highly applicable
- Applicable
- Poorly applicable

2) Were the interventions in the included studies applicable to the decision context?
- Highly applicable
- Applicable
- Poorly applicable

3) Was the included outcome not a surrogate outcome?
- Yes
- No

4) Was the outcome timeframe sufficient?
- Sufficient
- Insufficient

5) Were the conclusions based on direct comparisons?
- Yes
- No

Imprecision

1) Was the confidence interval for the pooled estimate not consistent with benefit and harm?
- Yes
- No

2) What is the magnitude of the median sample size?
- High (e.g. 300 participants)
- Intermediate (e.g. 100-300 participants)
- Low (e.g. <100 participants)

3) What was the magnitude of the number of included studies?
- Large (e.g. >10 studies)
- Moderate (e.g. 5-10 studies)
- Small (e.g. <5 studies)

4) Was the outcome a common event (e.g. occurs more than 1/100)?
- Yes
- No
- Not applicable (i.e. not a dichotomous outcome)

Further optional question for those engaged in guideline development[6]

5) Was there no evidence of serious harm associated with treatment?

- Yes
- No

Publication Bias (other considerations)

1) Did the authors conduct a comprehensive search?

- Yes
- No

2) Did the authors search for grey literature?

- Yes
- No

3) Authors did not apply restrictions to study selection on the basis of language?

- Yes
- No

4) There was no industry influence on studies included in the review?

- Yes
- No

5) There was no evidence of funnel plot asymmetry?

- Yes
- No
- Unclear

6) There was no discrepancy in findings between published and unpublished trials?

- Yes
- No
- Unclear

[6] This reflects GRADE guidance that guideline developers may use a less stringent threshold for judging imprecision of an intervention's benefits when there is no evidence of harm compared with when judging the benefits of an intervention where there is strong evidence of harm

Supplementary material 3: Applied QUIPS tool and Risk of Bias

Domain	Items for consideration	Rating
Study participation	Adequate description of period + place of recruitment Adequate description of in/exclusion criteria Adequate description of number + characteristics of study participants	**High risk:** Significant amount of eligible patients not included in the study (e.g., experimental design) **Low risk:** almost all eligible patients included or random inclusion
Intervention described	Adequate description of how adherence intervention was formulated, defined, or described.	**High risk**: no clear description for the medication adherence intervention **Low risk:** A clear description of the intervention and how it was measured, including the limitations
Outcome measurement	Clear definition of the study outcomes. Method of measurement described	**High risk:** flexible definition including interruptions or depending on time of data collection with different time points. **Low risk:** strict medication adherence definition with clear defined outcomes and related measurements
Sample and sample size	Sample has been described and where applicable, Sufficient sample size and/or rationale on how sample size was calculated.	**High risk:** no description of the sample and sample size reported, and no scientific justification for small or unmatching sample size **Low risk:** Sample has been described and where applicable sample size has been reported and sample size calculations provided
Overall (matched with EPHPP scores)		**High risk:** If 2 or more high risks **Moderate risk:** if 1 high risk and / or 2 or more unclear **Low risk:** If maximum 1 unclear and no high risks

Supplementary material 4_EPHPP_Quality Assessment Tool for quantitative studies

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1. Very likely
2. Somewhat likely
3. Not likely
4. Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1. 80 - 100% agreement
2. 60 – 79% agreement
3. less than 60% agreement
4. Not applicable
5. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

1. Randomized controlled trial
2. Controlled clinical trial
3. Cohort analytic (two group pre + post)
4. Case-control
5. Cohort (one group pre + post (before and after))
6. Interrupted time series
7. Other specify _____
8. Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?

1. Yes
2. No
3. Can't tell

The following are examples of confounders: Race

1. Sex
2. Marital status/family
3. Age
4. SES (income or class)
5. Education
6. Health status
7. Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

1. 80 – 100% (most)
2. 60 – 79% (some)
3. Less than 60% (few or none)
4. Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1. Yes
2. No
3. Can't tell

(Q2) Were the study participants aware of the research question?

1. Yes
2. No
3. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1. Yes
2. No
3. Can't tell

(Q2) Were data collection tools shown to be reliable?

1. Yes
2. No
3. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1. Yes
2. No
3. Can't tell
4. Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1. 80 -100%
2. 60 - 79%
3. less than 60%
4. Can't tell
5. Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

1. 80 -100%
2. 60 - 79%
3. less than 60%
4. Can't tell

(Q2) Was the consistency of the intervention measured?

1. Yes
2. No
3. Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

1. Yes
2. No
3. Can't tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one) community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one) community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

1. Yes
2. No
3. Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

1. Yes
2. No
3. Can't tell

GLOBAL RATING

COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	SELECTION BIAS	STRONG	MODERATE	WEAK	
		1	2	3	
B	STUDY DESIGN	STRONG	MODERATE	WEAK	
		1	2	3	
C	CONFOUNDERS	STRONG	MODERATE	WEAK	
		1	2	3	
D	BLINDING	STRONG	MODERATE	WEAK	
		1	2	3	
E	DATA COLLECTION METHOD	STRONG	MODERATE	WEAK	
		1	2	3	
F	WITHDRAWALS AND DROPOUTS	STRONG	MODERATE	WEAK	
		1	2	3	Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):

1	STRONG	(no WEAK ratings)
2	MODERATE	(one WEAK rating)
3	WEAK	(two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1. Oversight
2. Differences in interpretation of criteria
3. Differences in interpretation of study

Final decision of both reviewers (circle one):

1. STRONG
2. MODERATE
3. WEAK

Supplementary material 5_Search term strategy

PUBMED

1	"HIV Treatment" OR "Antiretroviral Therapy" OR "Antiretroviral Treatment" OR "ART treatment" OR "ART adherence" OR "ART Programs" OR "ART Programmes" OR "Mellitus Diabetes" OR "Hypertension" OR "Hypertension treatment" OR "Hypertension treatment adherence" OR “Stroke” OR "Chronic conditions" AND "Adherence" OR "Compliance" AND "Intervention" OR "Strategies" OR "Odds ratio" OR "risk ratio" OR "Evaluation" OR "Impact" OR "Effectiveness" OR "Outcome" AND "sub-Saharan Africa" OR "sub Saharan Africa" OR "sub-Saharan African" OR "sub Saharan African" OR "Sub-Saharan Africa" OR "Africa" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cabo Verde" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Democratic Republic of Congo" Or "Congo Republic" OR "Cote D'ivoire" OR "Equatorial Guinea" OR "Eritrea" OR "Eswatini" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Madagascar" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome And Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe"[MeSH Terms]
2	"HIV Treatment"[Title/Abstract] OR "Antiretroviral Therapy"[Title/Abstract] OR "Antiretroviral Treatment"[Title/Abstract] OR "ART treatment"[Title/Abstract] OR "ART adherence"[Title/Abstract] OR "ART Programs"[Title/Abstract] OR "ART Programmes"[Title/Abstract] OR "Mellitus Diabetes"[Title/Abstract] OR "Hypertension"[Title/Abstract] OR "Hypertension treatment"[Title/Abstract] OR "Hypertension treatment adherence"[Title/Abstract] OR "Chronic conditions"[Title/Abstract] OR "Stroke"[Title/Abstract] AND "Adherence"[Title/Abstract] OR "Compliance"[Title/Abstract] AND "Intervention"[Title/Abstract] OR "Strategies"[Title/Abstract] OR "Odds ratio"[Title/Abstract] OR "risk ratio"[Title/Abstract] OR "Evaluation"[Title/Abstract] OR "Impact"[Title/Abstract] OR "Effectiveness"[Title/Abstract] OR "Outcome"[Title/Abstract] AND "sub-Saharan Africa"[Title/Abstract] OR "sub Saharan Africa"[Title/Abstract] OR "sub-Saharan African"[Title/Abstract] OR "sub Saharan African"[Title/Abstract] OR "Sub-Saharan Africa"[Title/Abstract] OR "Africa"[Title/Abstract] OR "Angola"[Title/Abstract] OR "Benin"[Title/Abstract] OR "Botswana"[Title/Abstract] OR "Burkina Faso"[Title/Abstract] OR "Burundi"[Title/Abstract] OR "Cabo Verde"[Title/Abstract] OR "Cameroon"[Title/Abstract] OR "Central African Republic"[Title/Abstract] OR "Chad"[Title/Abstract] OR "Comoros"[Title/Abstract] OR "Democratic Republic of Congo"[Title/Abstract] OR "Congo Republic"[Title/Abstract] OR "Cote D'ivoire"[Title/Abstract] OR "Equatorial Guinea"[Title/Abstract] OR "Eritrea"[Title/Abstract] OR "Eswatini"[Title/Abstract] OR "Ethiopia"[Title/Abstract] OR "Gabon"[Title/Abstract] OR "Gambia"[Title/Abstract] OR "Ghana"[Title/Abstract] OR "Guinea"[Title/Abstract] OR "Guinea-Bissau"[Title/Abstract] OR "Kenya"[Title/Abstract] OR "Lesotho"[Title/Abstract] OR "Liberia"[Title/Abstract] OR "Madagascar"[Title/Abstract] OR "Malawi"[Title/Abstract] OR "Mali"[Title/Abstract] OR "Mauritania"[Title/Abstract] OR "Mauritius"[Title/Abstract] OR "Mozambique"[Title/Abstract] OR "Namibia"[Title/Abstract] OR "Niger"[Title/Abstract] OR "Nigeria"[Title/Abstract] OR "Rwanda"[Title/Abstract] OR "Sao Tome[Title/Abstract] OR Principe"[Title/Abstract] OR "Senegal"[Title/Abstract] OR "Seychelles"[Title/Abstract] OR "Sierra Leone"[Title/Abstract] OR "Somalia"[Title/Abstract] OR "South Africa"[Title/Abstract] OR "South Sudan"[Title/Abstract] OR "Sudan" "Tanzania"[Title/Abstract] OR "Togo"[Title/Abstract] OR "Uganda"[Title/Abstract] OR "Zambia"[Title/Abstract] OR "Zimbabwe"[Title/Abstract]
3	(English[Language])
4	(("2000/01/01"[Date - Publication] : "2022/11/01"[Date - Publication]))
5	1 OR 2

WEB OF SCIENCE

1	ALL=('HIV Treatment' OR 'Antiretroviral Therapy' OR 'Antiretroviral Treatment' OR 'ART treatment' OR 'ART adherence' OR 'ART Programs' OR 'ART Programmes' OR 'Mellitus Diabetes' OR 'Mellitus Diabetes treatment' OR 'Mellitus Diabetes adherence' OR 'Hypertension' OR 'Hypertension treatment' OR 'Hypertension treatment adherence' OR 'Chronic conditions' AND 'Adherence' OR 'Compliance')
2	Publication Years: 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 or 2014 or 2013 or 2012 or 2011 or 2010 or 2009 or 2008 or 2007 or 2006 or 2005 or 2004 or 2003 or 2002 or 2001 or 2000
3	Languages: English.
4	Citation Topics Meso: 1.26 Diabetes or 1.66 Hiv or 1.55 Urology & Nephrology - General or 1.37 Cardiology - General or 1.44 Nutrition & Dietetics or 1.104 Virology - General or 1.105 Strokes or 1.156 Healthcare Policy or 1.155 Medical Ethics or 1.112 Palliative Care or 4.13 Telecommunications.
5	Research Areas: Cardiovascular System Cardiology or General Internal Medicine or Infectious Diseases or Immunology or Health Care Sciences Services or Research Experimental Medicine or Nutrition Dietetics or Science Technology Other Topics or Respiratory System or Virology or Nursing or Biomedical Social Sciences or Social Sciences Other Topics or Religion or Government Law or Family Studies or Education Educational Research or Telecommunications or Ethnic Studies or Social Issues or Communication.
6	Countries/Regions: SOUTH AFRICA or ETHIOPIA or UGANDA or NIGERIA or KENYA or TANZANIA or GHANA or ZIMBABWE or ZAMBIA or MALAWI or CAMEROON or MOZAMBIQUE or BOTSWANA or DEM REP CONGO or RWANDA or SUDAN or COTE IVOIRE or BURKINA FASO or LESOTHO or NAMIBIA or SENEGAL or ESWATINI or BENIN or REP CONGO or SOMALIA or TOGO or BURUNDI or MALI or GUINEA or GABON or LIBERIA or MAURITIUS or ANGOLA or GUINEA BISSAU or NIGER or SIERRA LEONE or ERITREA or GAMBIA or SEYCHELLES or SOUTH SUDAN or CAPE VERDE or CHAD or COTE D IVOIRE or MADAGASCAR.
7	Open Access:Gold or Gold-Hybrid or All Open Access or Free to Read or Green Published or Green Accepted or Green Submitted
8	Web of Science Categories: Infectious Diseases or Medicine General Internal or Immunology or Multidisciplinary Sciences or Health Care Sciences Services or Public Environmental Occupational Health or Cardiac Cardiovascular Systems or Virology or Peripheral Vascular Disease or Social Sciences Biomedical or Health Policy Services or Microbiology or Medicine Research Experimental or Nutrition Dietetics or Pharmacology Pharmacy or Respiratory System or Primary Health Care or Psychology Multidisciplinary or Medical Informatics or Nursing or Social Sciences Interdisciplinary or Tropical Medicine or Family Studies or Biology or Social Work or Clinical Neurology or Computer Science Information Systems or Economics or Education Scientific Disciplines or Ethics or Green Sustainable Science Technology or Medical Ethics or Psychiatry or Radiology Nuclear Medicine Medical Imaging or Reproductive Biology or Biochemical Research Methods or Education Educational Research or Food Science Technology or Physiology or Political Science or Psychology Applied or Psychology Clinical or Psychology Social or Public Administration or Telecommunications or Toxicology.

CINAHL

1	"HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
2	Limiters - Published Date: 20000101-20221131; English Language; Human; Age Groups: All Adult; Geographic Subset: Africa; Language: English
3	Expanders - Also search within the full text of the articles; Apply equivalent subjects
4	Search modes - Find all my search terms
5	Expanders - Apply equivalent subjects
	Narrow by SubjectGeographic - Africa
6	Search modes - Boolean/Phrase

SCOPUS

1	TITLE-ABS-KEY ("HIV Treatment" OR "Antiretroviral Therapy" OR "Antiretroviral Treatment" OR "ART treatment" OR "ART adherence" OR "ART Programs" OR "ART Programmes" OR "Mellitus Diabetes" OR "Hypertension" OR "Hypertension treatment" OR "Hypertension treatment adherence" OR "Chronic conditions" OR "Stroke" AND "Adherence" OR "Compliance" AND "Intervention" OR "Strategies" OR "Odds ratio" OR "risk ratio" OR "Evaluation" OR "Impact" OR "Effectiveness" OR "Outcome" AND "sub-Saharan Africa" OR "sub Saharan Africa" OR "sub-Saharan African" OR "sub Saharan African" OR "Sub-Saharan Africa" OR "Africa" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cabo Verde" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Democratic Republic of Congo" OR "Congo Republic" OR "Cote D'ivoire" OR "Equatorial Guinea" OR "Eritrea" OR "Eswatini" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Madagascar" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome And Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe")
2	(LIMIT-TO (LANGUAGE , "English")

3	AND (LIMIT-TO (OA , "all") OR LIMIT-TO (OA , "publisherfullgold") OR LIMIT-TO (OA , "publisherhybridgold") OR LIMIT-TO (OA , "publisherfree2read") OR LIMIT-TO (OA , "repository"))
4	(LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002))
5	(LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "DECI") OR LIMIT-TO (SUBJAREA , "HEAL") OR LIMIT-TO (SUBJAREA , "IMMU") OR LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "PSYC") OR LIMIT-TO (SUBJAREA , "MULT") OR LIMIT-TO (SUBJAREA , "SOCI") OR LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "ENVI"))
6	(LIMIT-TO (AFFILCOUNTRY , "Uganda") OR LIMIT-TO (AFFILCOUNTRY , "South Africa") OR LIMIT-TO (AFFILCOUNTRY , "Tanzania") OR LIMIT-TO (AFFILCOUNTRY , "Zambia") OR LIMIT-TO (AFFILCOUNTRY , "Zimbabwe") OR LIMIT-TO (AFFILCOUNTRY , "Kenya") OR LIMIT-TO (AFFILCOUNTRY , "Malawi") OR LIMIT-TO (AFFILCOUNTRY , "Nigeria") OR LIMIT-TO (AFFILCOUNTRY , "Togo") OR LIMIT-TO (AFFILCOUNTRY , "Cameroon") OR LIMIT-TO (AFFILCOUNTRY , "Cote d'Ivoire") OR LIMIT-TO (AFFILCOUNTRY , "Mozambique") OR LIMIT-TO (AFFILCOUNTRY , "Ethiopia") OR LIMIT-TO (AFFILCOUNTRY , "Burkina Faso") OR LIMIT-TO (AFFILCOUNTRY , "Ghana") OR LIMIT-TO (AFFILCOUNTRY , "Senegal") OR LIMIT-TO (AFFILCOUNTRY , "Benin") OR LIMIT-TO (AFFILCOUNTRY , "Botswana") OR LIMIT-TO (AFFILCOUNTRY , "Democratic Republic Congo") OR LIMIT-TO (AFFILCOUNTRY , "Rwanda") OR LIMIT-TO (AFFILCOUNTRY , "Swaziland") OR LIMIT-TO (AFFILCOUNTRY , "Congo") OR LIMIT-TO (AFFILCOUNTRY , "Gabon") OR LIMIT-TO (AFFILCOUNTRY , "Guinea") OR LIMIT-TO (AFFILCOUNTRY , "Lesotho") OR LIMIT-TO (AFFILCOUNTRY , "Mauritania") OR LIMIT-TO (AFFILCOUNTRY , "Niger"))

GOOGLE SCHOLAR

	With all of the words	With at least one of the words
1	allintitle: Antiretroviral Therapy AND Adherence OR Intervention	"HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR

		“Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
2	allintitle: Antiretroviral Treatment AND Adherence OR Intervention	"HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
3	allintitle: ART AND Adherence OR Intervention	""HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR

		“Burundi” OR “Cabo Verde” OR “Cameroon” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
4	allintitle: Mellitus Diabetes AND Adherence OR Intervention	"HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
5	allintitle: Hypertension AND Adherence OR Intervention	"HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon”

		OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
6	allintitle: Hypertension treatment AND Adherence OR Intervention	"HIV Treatment" OR “Antiretroviral Therapy” OR "HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
7	allintitle: Hypertension therapy AND Adherence OR Intervention	"HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon”

		OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
8	allintitle: Chronic conditions AND Adherence OR Intervention	"HIV Treatment" OR “Antiretroviral Therapy” OR “Antiretroviral Treatment” OR “ART treatment” OR “ART adherence” OR “ART Programs” OR “ART Programmes” OR “Mellitus Diabetes” OR “Hypertension” OR “Hypertension treatment” OR “Hypertension treatment adherence” OR “Chronic conditions” OR “Stroke” AND “Adherence” OR “Compliance” AND “Intervention” OR “Strategies” OR “Odds ratio” OR “risk ratio” OR “Evaluation” OR “Impact” OR “Effectiveness” OR “Outcome” AND “sub-Saharan Africa” OR “sub Saharan Africa” OR “sub-Saharan African” OR “sub Saharan African” OR “Sub-Saharan Africa” OR “Africa” OR “Angola” OR “Benin” OR “Botswana” OR “Burkina Faso” OR “Burundi” OR “Cabo Verde” OR “Cameroon” OR “Central African Republic” OR “Chad” OR “Comoros” OR “Democratic Republic of Congo” Or “Congo Republic” OR “Cote D'ivoire” OR “Equatorial Guinea” OR “Eritrea” OR “Eswatini” OR “Ethiopia” OR “Gabon” OR “Gambia” OR “Ghana” OR “Guinea” OR “Guinea-Bissau” OR “Kenya” OR “Lesotho” OR “Liberia” OR “Madagascar” OR “Madagascar” OR “Malawi” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Mozambique” OR “Namibia” OR “Niger” OR “Nigeria” OR “Rwanda” OR “Sao Tome And Principe” OR “Senegal” OR “Seychelles” OR “Sierra Leone” OR “Somalia” OR “South Africa” OR “South Sudan” OR “Sudan” “Tanzania” OR “Togo” OR “Uganda” OR “Zambia” OR “Zimbabwe”
9	Language	English
10	Custom range	2000-2022

CHAPTER 8

GENERAL DISCUSSION

The overarching objectives of this study were to contribute evidence that can provide guidance regarding the barriers to and facilitators of adherence for people living with HIV (PLHIV) on first-line and second-line antiretroviral therapy (ART) and describe the different adherence strategies that were utilized. As described in the protocol study reported in chapter 2, we used an integrated multilevel socio-ecological framework, to determine the influence of the multiple factors that impact adherence to ART and the continuum of HIV care in rural and urban communities. This general discussion presents the main findings of this thesis which focuses on addressing these five research questions.

1. What is the uptake rate of ART, and the individual-level predictors of virological failure and being lost to follow-up (LTFU) in PLHIV taking ART in urban communities?
2. What are the individual-level factors that predict virological failure, low CD4 count, and retention in care for patients on second-line ART in urban communities?
3. What are the individual, relationship or interpersonal, and community-level factors associated with self-reported adherence, pill count, and virological failure to ART in rural communities?
4. What are the different treatment-taking behaviours and perspectives on adherence to ART between virally suppressed and unsuppressed patients on second-line ART in urban communities?
5. What treatment adherence strategies and interventions have been implemented and evaluated in sub-Saharan Africa for ART, hypertension, and Diabetes Mellitus?

After reporting the main findings, the implications thereof on the barriers and facilitators of adherence to ART for PLHIV receiving ART are discussed. Subsequently, the strengths and limitations of this thesis, the directions for future research, and the conclusions are discussed.

ART uptake and predictors of virological failure and LTFU

In the retrospective data analysis for patients on first-line and second-line ART in the study reported in chapter 3, we described the overall demographics and treatment information of a large cohort initiating first-line and second-line ART regimens in Johannesburg. We further identified demographic and clinical characteristics such as age, gender, CD4 count, and ART regimen that predict virological failure and patients LTFU. To our knowledge, this is one of the largest studies to date from the South African national HIV treatment program reporting on ART uptake, virological failure, and retention in care. Therefore, findings from this study can meaningfully contribute to the successful implementation or strengthening of ART support and adherence strategies, as well as highlighting where treatment support strategies need to be prioritized.

Of the total patients initiated on ART between 2004 and 2020, 12% were initiated on the d4T/3TC+EFV combination, 16% were initiated on TDF/3TC/EFV combination, and 59% on fixed dose combination (FDC) (TDF/FTC/EFV). Zidovudine accounted for 3% of regimens over the 16

years. Since the substitution of efavirenz (EFV) with dolutegravir (DTG) as of September 2019, fewer than 1500 patients were either initiated or switched to a DTG-containing regimen by the end of February 2020. This accounted for 1% of the study cohort who were initiated or switched to a DTG-based regimen in less than 6 months (between September 2019 and February 2020). The transition to a DTG-based regimen in South Africa has been effected in a phased approach, and the number of patients initiating DTG was expected to increase in subsequent years. The phased approach was adopted to adequately monitor the potential risks. These include drug-to-drug interactions and unwanted adverse effects that need to be considered against the potential benefits of the drug [1]. As of March 2023, over 4,5 million patients in South Africa were receiving treatment combinations that include DTG [2]. Innovations in and development of ART have taken place largely in high-income regions [3]. New ART medication is often inaccessible immediately in low- and middle-income countries (LMICs) due to high prices and patent laws that prevent LMICs from manufacturing and exporting new ART drugs [3]. In addition, in high-income countries, the availability of resistance testing provides greater flexibility in what medication to initiate and a wider option of drugs, while providing close monitoring of side effects [3]. This is a more patient-centered approach to treatment resulting in, improved treatment outcomes [3].

In our analyses reported in chapter 3, patients on FDC were similarly more likely to achieve virological suppression and less likely to be LTFU. The simultaneous introduction of FDC and improvements in adherence interventions may have facilitated the improved treatment outcomes and decline of LTFU between 2013 and 2019 [4]. In addition, various studies have reported improved treatment outcomes and retention in care associated with FDC, also noting that the improvement extends beyond the single-pill versus multi-pill ART comparison, to availability of adherence support, time between medical visits, and patient waiting times [4,5]. This is particularly important because, besides the reported effects of FDC towards treatment adherence, the design and implementation of any adherence intervention should consider multiple factors that influence treatment-taking behaviour for it to yield the desired outcomes.

Patients who were 25 years and older, patients with a most recent CD4 cell count above 100 cells/µL, and patients who were initiated from 2011 onwards, were all more likely to achieve viral load suppression and remain in care. Since 2011, the South African ART program has seen improvements in ART regimens (e. g. changes from triple therapy to FDC in 2013) and CD4 cell count thresholds for treatment initiation (e.g. changes from 350 to 500 cells/µL in 2015). These have most likely contributed to better clinical outcomes [6]. These findings are consistent with other studies that reported that older patients who had higher CD4 cell counts and/ or initiated from 2011 onwards were more likely to obtain viral load suppression and to remain in care [7–12]. Therefore, patients under 25 years old and patients with a low CD4 cell count need to be prioritized for interventions that address treatment and adherence. Younger patients, as well as patients with a low CD4 cell count, have been previously identified as needing to be targeted in HIV program strengthening, as these population groups remain at higher risk of less

favourable treatment outcomes [7–12]. Our analyses reinforce that these population groups should be treated with urgency, given that the latest World Health Organization global report shows that the number of adolescent infections is rampant and continues to grow [13].

Overall, this study showed that most patients did well virologically but retention in care was poor. The outcomes observed in this study are similar to those of other studies in sub-Saharan African (SSA) countries [7–9] but different from most findings from high-income countries [14]. In general, compared with LMICs, high-income countries have reported better virological outcomes and retention rates [15,16]. In high-income countries, integrated models of care and efficient healthcare systems that are more patient-centered have been promoted thereby better meeting the needs of the patients [17]. However, poor health outcomes in LMIC are attributed to unequal distribution of resources, increased disease burden, high patient influx in public health facilities, shortage of skilled healthcare workers, and failure to adopt strategies employed by the government to improve the quality of healthcare services [18].

Patient and program monitoring can be improved by actively implementing adherence and retention programs. This would result in better quality of service delivery and improved accountability on the part of patients. Implementing and promoting adherence and retention strategies from the beginning of treatment can lead to better clinical outcomes and higher retention rates. Since the duration between clinic visits can be as long as six months, it is important to consider approaches that enable continued patient-provider engagement between these visits. This can be done by providing regular health gamification, videos, and health resources using mHealth platforms to promote retention [19].

Predictors of treatment outcomes among PLHIV on second-line ART

Second-line ART is complex, and patients failing on this regimen have very limited further treatment options available for them [20]. Although switching patients who experience treatment failure of first-line treatment to second-line regimens has been the standard policy in the South African public health setting [20], individual-level factors that predict virological failure and retention in care for patients on second-line ART are not fully identified.

In the study described in chapter 4, we found that being older predicted poor retention in care for patients on second-line ART, a finding that is inconsistent with previous findings from a similar setting [21]. Poor retention in care for older patients in this cohort could be suggestive of data quality issues in routine ART program data systems in South Africa. Data quality issues are common in ART programs and the absence of a single unique identifier for patients with HIV in South Africa contributes significantly to the reported proportion of patients not retained in ART [22,23]. Although the Department of Health tries to ensure good quality of data, data quality issues remain, in particular, due to inconsistencies in data recording, capturing, and missing information [24].

In the study presented in chapter 4**,** males and transferred-in patients both had lower CD4+ cell counts and greater virological failure. Also, the likelihood of patients on second-line ART older than 25 years achieving viral suppression grew incrementally compared to patients under 25 years. These findings corroborate other studies conducted in South Africa [15,16] and emphasize the importance of implementing appropriate adherence support mechanisms that are age-specific such as youth-friendly clinics, and which strengthen individual adherence counselling.

Overall, studies reported in chapters 3 and 4 exhibited that younger patients, male patients, and patients with low CD4 cell counts and on second-line ART must be considered when designing/implementing treatment support strategies and models to improve treatment outcomes and reduce LTFU, regardless of the ART regimen the patient is taking. Support strategies could include strengthening directed patient management from the commencement of ART and community-based interventions, such as youth-friendly clinics, male-friendly clinics, adherence clubs, and ART pick-up points, or using digital health technology innovations for patient engagement between clinic visits, appointments, and medication reminders and education.

Multilevel factors associated with adherence to ART

PLHIV in LMIC are often severely affected by disadvantaged socio-economic status, limited access to healthcare services, poor infrastructure, and healthcare resources. This situation may adversely affect access and adherence to HIV treatment, resulting in worse health outcomes for PLHIV. As these populations may have unique barriers to and facilitators of adherence to HIV treatment, the study reported in chapter 5 set out to perform a comprehensive assessment of socio-demographic, psychosocial, behavioural, and socio-economic risk factors for non-adherence as measured through self-report, pill count and virological failure among PLHIV, attending a healthcare facility in Limpopo, South Africa, in a rural and underserviced community. In the study reported in chapter 5, we identified several demographics, socio-economic, and behavioural risk factors for non-adherence and virological failure and showed that there was limited overlap of markers of adherence with virological failure. Over half the participants were aged 35-49 years and were in a relationship, which included being married, cohabiting, or having a partner but not living together. The majority had a secondary (grade 8-12) or tertiary level of education. 1 in 5 had not studied beyond a primary education level (grade 0-7).

We encountered high levels of self-reported adherence difficulties and suboptimal adherence, as measured through pill counts (pill count<95%). However, rates of virological failure in this cohort were more limited (15.6%). Self-reported adherence difficulties and suboptimal adherence as measured through pill count results were significantly correlated with each other and with virological failure. Various studies have reported significant correlations between objective and self-report measures of ART adherence, [25–27] even though some studies

conducted in both developed and developing settings, suggest that viral load is more likely to be accurate in reflecting true adherence rates than self-reported adherence. [28,29]. Previous research conducted in SSA countries has also found that self-reported adherence tended to provide inaccurate estimates of adherence, and is not necessarily associated with the virological suppression status of patients [30–33]. Factors that may affect the reliability of self-reported adherence and pill counts are numerous and include variations in measurement methods and thresholds, social desirability bias, healthcare worker trust, and recall error.

In multivariable analyses, we found that self-reported adherence difficulties, suboptimal pill count adherence, and virological failure were more likely in men than women. The finding that men experienced greater problems with ART adherence is consistent with other studies conducted in rural settings and may reflect poorer healthcare behaviour in men [7,8,10,11,34–38]. Several studies performed in different cultural contexts have identified underlying reasons for the generally poorer healthcare behaviour of men [4,57–59]. For men in rural settings in particular, these include lack of time, poor healthcare access due to social constructions of masculinity, underlying cultural reasons, the distance needed to travel to access care, and the lack of male care providers [4,15,57,58,60,61]. Such men report more severe barriers to care than their urban counterparts [13,62]. This highlights the need to acknowledge that not only do rural men's perceptions of masculinity serve as a barrier to accessing ART services, but that this group needs to be prioritized for ART adherence interventions [41].

That suboptimal adherence as indicated by the pill count reported in the study in chapter 5 was associated with low household income, which is also evidenced in other studies [47,48]. These findings confirm that despite the scale-up of free ART in South Africa, financial constraints remain a barrier to ART adherence. Concerns about low household income in rural settings are centered around the cost of seeking treatment, the distance needed to travel to access care, reliance on traditional medicine, and the cost of food [47]. At first sight, our finding that in stratified analysis the risk of virological failure was higher among male participants experiencing food insecurity seems to be a result of this same dynamic. However, this finding is at odds with other studies that have reported that women, not men, are less favoured in terms of household food distribution and that mechanisms for how food insecurity impacted adherence were generally similar among women and men [49,50]. Nonetheless, our results suggest that there is a link between sex, food insecurity, and ART adherence, heightening the importance of addressing food insecurity as part of comprehensive care among PLHIV. Further research should also examine how the negative impact of food unavailability on adherence in food-stressed households can be mitigated. A study reported in chapter 7 of this thesis highlights a few programmatic models that have been successful in sub-Saharan Africa, to improve food security and nutrition in an HIV context. These include 1) Nutrition supplementation interventions targeted to undernourished PLHIV, such as promoting the use of specialized foods, with nutrition assessment, counselling and support as a central component, and targeting all PLHIV regardless of nutrition status 2) Safety nets (food, cash

transfer or vouchers), targeting HIV-affected households and individuals (such as orphans and vulnerable children) to improve household food security together with mitigating the impact of HIV; and 3) Livelihood interventions such as informal businesses, agriculture, or animal husbandry targeting PLHIV households or communities heavily affected by the AIDS epidemic [51,52].

In the cohort studied in chapter 5, better adherence as indicated by pill count was associated with increased use of task-oriented coping. This was more evident in female participants. This suggests that counselling strategies addressing specific coping styles could have a positive effect on ART treatment outcomes. Moreover, likely, there are also indirect associations between coping strategies, sex, and treatment adherence. More research is needed to assess these relationships and guide future interventions.

Furthermore, we found that the risk of virological failure was higher among participants with moderate or severe depressive symptoms. These findings are comparable to those of several studies assessing risk factors for non-adherence in PLHIV, which also found evidence that depression was associated with poor outcomes for HIV-infected individuals on ART, especially in women [67,68]. Our results in chapter 5 suggest that, despite substantial progress made in quality and access to HIV-related healthcare [69] as observed with the recent transition to a DTG-based regimen, [70] depression and other mental health problems remain underdiagnosed and often untreated among rural PLHIV [45,57]. Hence, there remains a critical need to screen for and treat depressive symptoms in PLHIV. The association between depression, sex, and markers of suboptimal adherence, indicates that screening for mental health problems should be considered an integral part of adherence counselling and that treatment of these problems could potentially improve adherence to ART.

Overall, results reported in chapter 5 showed that there is a critical need to screen for and treat depressive symptoms in PLHIV, particularly those in rural areas. The association between depression, sex, and markers of suboptimal adherence observed in chapter 5 indicates that screening for mental health problems should be considered an integral part of adherence counselling and that treatment of these problems could potentially improve adherence to ART.

Treatment behaviours and perspectives of PLHIV on adherence to second-line ART

In chapter 6, we reported a cross-sectional study that sought to describe the different treatment-taking behaviours and perspectives of adherence to ART between virally suppressed and unsuppressed patients using second-line ART. This study shared the perspectives of patients experiencing virological failure, adherence challenges, and patients' recommendations to improve adherence, as not much is documented about the perspectives of patients who experience adherence challenges [58].

In the study reported in chapter 6, we found that single and unmarried people living with their partners were more likely to be virally unsuppressed. It has been reported that relationship dynamics influence ART adherence and viral load suppression, in that being married or having a committed and supportive partner tends to foster an environment for better clinical outcomes in HIV-positive people [59,60]. We noted viral load suppression in those participants who resided further away from the health facilities. This is incongruent with findings of studies conducted in Uganda, Ghana, and Burkina Faso [61–63], which reported that individuals who resided closer to a health facility were more likely to seek healthcare.

Late disclosure may hinder adherence or treatment support and subsequently yield poor clinical outcomes [64–67]. Whilst the majority of participants in chapter 6 (63%) disclosed their HIV status one week after diagnosis, about 28% took longer than four weeks to disclose to their partners and/or relatives. Early disclosure, particularly to a family member or partner, has been strongly associated with improved adherence [64–67]**.** In addition, disclosure to a family member or partner has been linked to adequate psychosocial support which in turn facilitates treatment adherence [65,67–70]. However, the findings in chapters 6 suggest that disclosure and dependence on a treatment supporter are not likely to produce desired adherence levels (and did not feature in the list of participant recommendations). This indicates that disclosure and treatment support should be assessed in combination with other adherence strategies instead of as a single consideration or mechanism [71].

Predictably, the toxicity level of second-line multi-pill regimens was seen as more difficult to bear, than consuming a daily single tablet or a well-tolerated FDC first-line regimen. These views were consistent with reports from other studies that attributed similar challenges to taking second-line regimens [29,72,73]. Participants who did not interrupt ART mainly reported using an alarm as a reminder to take their medication. This finding in chapter 6 suggests the need to explore external reminder mechanisms for improving adherence in this setting, considering that approximately 15% of participants experiencing virological failure reported not using any external reminders. Various studies conducted globally, have also found a trend towards better adherence amongst patients who used external reminders [74–76]. In addition, our study showed that participants who used their handbags to store their medication were more likely to adhere to treatment. This finding is congruent with other studies that have reported having a handbag to have pills on hand all the time, was participants' preferred ART storage practice [77–79].

Side effects are an important predictor of poor adherence, and cumulative toxicity associated with ART, especially in second-line regimens usually are responsible for the adverse reactions or side effects [80–83]. We found that participants experiencing virological failure were more likely to have treatment-related side effects. In the study reported in chapter 6, participants with side effects were also more likely to be unemployed. Although this was not explored further in our study, various studies have reported that employed participants can manage

their health and side effects better than their unemployed counterparts [84–86]. This is attributed to enhanced personal capacity, self-esteem, self-efficacy, and improved quality of life associated with being employed [87]. However, there is limited evidence on the effect of employment on health outcomes, with some studies showing no effect of employment on health [88]. While unemployment is almost universally linked to poor outcomes, employment may be positive or negative, depending on the nature of the employment, for example, stability of employment, stress related to the type of work, working hours, and salary [88].

Participants had recommendations on drug formulation that may improve adherence among PLHIV on second-line regimens. These included an FDC second-line ART dosage that is taken once a day and reducing the pill size. Furthermore, the participants suggested that education on the benefits of taking ART could improve adherence, whilst a few participants also suggested the implementation of injectable second-line ART.

Intervention strategies to improve adherence to ART

Chapter 7 was the systematic review that assessed treatment adherence interventions for established and emerging chronic conditions in SSA (HIV, Hypertension, and Diabetes Mellitus). The aim of the review was to identify successful adherence interventions that could be transferred across health conditions and employed in the South African HIV program This review provided useful comparisons and context to adherence intervention strategies for the chronic conditions in SSA. Although numerous reviews have evaluated adherence interventions [89–93], few have undertaken a comparative analysis of adherence to medication for various conditions, notably HIV, hypertension, and diabetes mellitus. Although HIV is still the leading cause of death in SSA, the burden of non-communicable diseases, especially hypertension and diabetes mellitus, has increased in the last decade [94–96], and therefore, understanding adherence to related medication is a priority issue.

There has been a significant increase in the number of studies implementing and evaluating interventions aimed at promoting adherence to chronic conditions. This systematic review combined the available evidence from a large number of studies to identify a range of adherence interventions aimed at promoting adherence to ART among HIV-infected patients, anti-hypertensive medication, and anti-diabetic medication. The majority of adherence interventions described in our review were ART-related. This is consistent with health programs in most SSA countries, where focusing on HIV programs takes precedence over hypertension and diabetes mellitus-related programs. This approach is in contrast to that of most high-income countries whose focus has been balanced across the three chronic conditions [97–100]. Individual or patient-related characteristics described in the reviewed studies in chapter 7, demonstrated that almost two-thirds were females, and were of middle age [30-40 years]. The individual-specific characteristics identified may represent the demographic profile of patients in chronic treatment programs, particularly those receiving HIV care in SSA [101,102].

A majority of the studies included in the review in chapter 7 reported improved adherence, based on adherence measurements used. However, one in four studies reported no improvement in medication adherence based on the adherence measurements used, and most of these were community and home-based adherence interventions. Notwithstanding this, community-based adherence interventions demonstrated their potential value by serving as an important link between primary healthcare facilities or services and the communities; being able to support treatment integration and holistic patient care; and, advancing the decentralization of chronic care to the communities [103,104]. This includes peer treatment support, community-based social network support, and nutrition support. These community and home-based adherence interventions meet the rising need associated with overall chronic care, where due to the shortage of healthcare workers and the growing caseload of people needing care, professional healthcare workers' roles are increasingly limited to medical and nursing tasks [105]. This review provides evidence of the efficacy of community and home-based adherence support strategies but notes that more focus should be on their acceptability and cost-effectiveness.

Mobile health (mHealth) is increasingly being explored for health promotion [106] and was also used in adherence-promoting interventions analyzed in this review, to deliver educational and behavioural components, either singly or in combination. The majority of mhealth related medication adherence interventions reported improved adherence using specified outcome measurements. Most mhealth interventions were used to educate, remind, or provide advice to patients. These technologies enabled the collection and transfer of patient-specific data/information to different professionals, who could then deliver tailored feedback and reminders to the patients. The increasing advancement in technology and related benefits received by patients from healthcare providers without presenting at a health facility is an appealing prospect. Furthermore, mhealth interventions could have a greater reach, better adoption, and implementation, consequently having a greater positive health impact [106,107]. However, more research is needed to establish the sustainability of such interventions, particularly related to confidentiality, mobile data-related costs, compatibility with mhealth/digital solutions, and cell phones required, and to evaluate how mhealth interventions can be useful in the short and long term in promoting adherence to medications.

The interventions described in chapter 7 were primarily directed at patients and ranged from adherence counselling including both individual and group counselling, to more complex interventions such as mhealth ones. mHealth interventions took into consideration patients' abilities to use digital technology and preferences, in addition to educating and aiding them to adhere to medication. Some of the interventions were multifaceted employing a combination of interventions, like the combined use of educational, behavioural, or affective strategies. Behavioural and affective strategies, which are increasingly being used in adherence support interventions, range from adherence aids (such as medication administration aids), to motivational interviewing [108,109].

Individual and group counselling adherence interventions could be regarded as being more patient-centered, however, their impact depends on the extent to which patients' or individuals' psychosocial needs are considered. This includes attitudes towards the health condition, cultural barriers, social concerns (such as perceived stigma), and cognitive abilities. These needs have been recognized in recent years as important predictors of optimal adherence to treatment and should be considered in any development of adherence interventions for chronic conditions [110].

The role of healthcare service-related interventions on medication adherence has been emphasized, particularly in cases of chronic diseases, [111] though their impact is difficult to measure and has often been found to be inconsistent [111,112]. Many adherence intervention strategies have also addressed healthcare services-related factors impacting adherence, as was seen in this review. These include patient-related, condition-related, and medication-related factors. For example, this review reported that adopting and using better ART drugs improved medication adherence. In addition, greater emphasis on task-shifting and decentralization of services improved medication adherence and is worthy of further investigation.

This review also reported improved medication adherence and retention in care for participants who received cash vouchers during the study period. The early positive effects of financial incentives on adherence and retention were sustained in the group that received cash vouchers after the intervention was complete. Although this intervention improved adherence, the effect of such interventions should be considered along with other tested interventions, as part of a comprehensive package of support during the treatment journey. A larger-scale impact evaluation to determine the practicality of cash support on cost-effectiveness, and issues related to sustainability also needs consideration.

There is larger evidence in chapter 7 that community-and home-based, mhealth and adherence counselling interventions can improve adherence to ART. Therefore, these tested adherence-enhancing interventions should increasingly be considered for routine implementation in health programs. However, rigorous ongoing evaluation of the impact and performance of these interventions will be critical.

Human behaviour in itself is a complex phenomenon. It is, therefore, more likely that any intervention designed to influence human behaviour, such as modifying medication adherence in patients with chronic conditions, would be more successful if multiple factors that aid the change in complex human behaviour are addressed. Combined interventions comprise different components, which may act both independently and inter-dependently, to address the changes needed, and may be more effective than using a single component in isolation [113]. However, the complexity involved in designing, implementing, evaluating, and

replicating. 'combined intervention(s)', often complicates the practicalities of such interventions [113]. Therefore, interventions involving a single component may be preferred as they are easier to design, implement and replicate, and oftentimes are successful in influencing a behaviour change [113].

Strengths, limitations, and directions for future research

To our knowledge this was the first research to use a socio-ecological framework, HIV care continuum model, and various study designs to report on the barriers and facilitators to ART adherence and HIV care cascade for PLHIV in rural and urban communities of South Africa. Combining multi-level models and reports from other chronic disease programs in SSA, the evidence from the studies presented in this thesis enabled us to identify the barriers to and facilitators of adherence for PLHIV on first-line and second-line antiretroviral therapy and make recommendations for comprehensive, acceptable, and appropriate intervention strategies to improve treatment adherence.

The methodological approach also ensured that a total sample size of 173 842 people was included across all studies reported in this thesis. With such a large sample size a strong body of evidence was created reporting on barriers to and facilitators of ART adherence and adherence intervention strategies implemented. This should allow the findings to be extrapolated for making recommendations for comprehensive, acceptable, and appropriate ART adherence strategies.

For data collection, the study reported in chapter 5 used validated tools to collect data. This included tools adapted from the South African National Income Dynamics Study and the National Health Nutrition Survey [114,115], the AIDS Clinical Trials Group (ACTG) questionnaire [116], the Brief Estimate of Health Knowledge and Action (BEHKA) HIV version [117], the Revised Helping Alliance Questionnaires [118], the Coping Inventory for Stressful Situations (CISS-21) [119,120], The 9-item Patient Health Questionnaire (PHQ) [121]. However, the study reported in chapter 6 did not use a validated questionnaire, as a result of this, the study results may have been affected by measurement error and reporting bias. To avoid or reduce measurement error and reporting bias in the study reported in chapter 6, we provided the study participants with clear study information and encouraged them to respond to study questions truthfully and as unbiased as possible. In addition, we verified the accuracy of the data collected by checking participants' medical records as part of data quality checks for the study. To further adjust for confounding bias in this study, multivariable logistic regression models were also built to identify independent predictors.

All the research studies included in this thesis were conducted in a total of eight health facilities (seven of over 120 health facilities in one South African metropolitan municipality (urban setting) and one facility in a rural setting). While this ensured that study participants had comparable demographic profiles throughout the different studies in this thesis, these findings

may not be generalizable to other regions or municipalities in South Africa, or other country settings. Nonetheless, studies reported in this thesis consisted of adequate study sample sizes to strengthen the effects of the findings. In addition, the direction and size of effect were generally consistent across all chapters, suggesting that the study findings may be robust despite all these limitations.

Furthermore, although the Department of Health tries to ensure good quality of data in Tier.Net, we did encounter quality issues in the studies presented in chapters 3 and 4. In particular, due to data inconsistencies and missing information (TIER.Net only records the most recent VL count which overrides the previously captured value), we could not accurately calculate time to VL suppression or failure with only one VL reading available. A standard VL result of 124 copies/mL is captured in TIER.Net for patients whose laboratory results are reported as lower than detectable level. This made it difficult to differentiate between patients who had an absolute value of VL results as '124' and those who had VL results as 'lower than detectable level'. This affected the calculated VL values such as the exact average VL count for the cohorts. TIER.Net does not enable linking records between health facilities which resulted in a lack of documentation of a large proportion of transfers. For chapter 3, it is plausible that this limitation in data increased during the 16-year study window as more facilities offering ART services became available for patients to transfer between. Deaths and LTFU are poorly recorded on TIER.Net, therefore, death and LTFU rates may be generally higher than reported in this study. While the LTFU has increased and a lot of patients who missed their appointments were regarded as LTFU after 90 days without medication, it is possible that some of these patients regarded as LTFU are receiving healthcare services at other facilities (self-transfer out)[14]. The association between lower CD4 count and increased LTFU could be explained as the lower CD4 count (and accompanying poor health) resulted in unrecorded deaths subsequently contributing to the increased LTFU. Filing systems for paper-based records in many public health facilities in the study setting are inadequate. Therefore, it is possible that some files were misplaced or not available for back capture. However, to maximize the captured records, information was captured from patient files and the ART longitudinal paper-based register which was used in the public health setting before the TIER.Net electronic version was implemented.

Studies reported in chapters 5 and 6 assessed a broad range of psychosocial factors, the many individual, social, and structural factors that may be of influence cannot feasibly be assessed in single studies. Therefore, the scope of covariates, while broad, by definition, inevitably is limited. In both studies, potential covariates of ART adherence were assessed through self-report, which may have been affected by memory bias and social desirability bias. Chapter 5 also highlighted the practical limitations of conducting pill counts. In many cases, patients forget to take their leftover medication to their clinical visit. Previous studies used unannounced pill count to avoid this practical limitation, but this may not be feasible in practice. To control for some of these limitations in both chapters, information such as viral

load, side effects, and comorbidity was verified by checking participants' medical records as part of data quality checks.

A limitation of the review described in chapter 7 is the lack of ability to compare intervention types quantitatively. Due to the heterogeneity of intervention designs, and the fact that many interventions were multifactorial, no direct cross-comparison or multivariable analysis was possible, and nor were we able to quantify regional variation in adherence success.

CONCLUSION

The studies presented in this thesis demonstrated that various factors that affect adherence to ART are important, as aligned with the socio-ecological conceptual framework. By populating this framework through various study methods, this thesis provided evidence on factors affecting treatment adherence across the various socio-ecological levels and context-specific intervention strategies to improve ART adherence. Our research found that many factors influence the ability to successfully engage individuals in HIV care. These factors include male patients, younger patients, patients experiencing ART-related side effects, patients experiencing moderate or severe depressive symptoms, patients with low household income, and food insecurity. Our results suggest that there is a link between low household income, food insecurity, and ART adherence, heightening the importance of addressing these issues as part of comprehensive care among PLHIV. Support strategies could include directed patient management from the commencement of ART, community-based interventions, such as adherence clubs, ART pick-up points, and nutritional support programs, or using digital health technology innovations for patient engagement between clinic visits, appointment, and medication reminders and education. Further research should also examine how the negative impact of food unavailability on adherence in food-stressed households can be mitigated. Our findings also showed that there is an important need to screen for and treat depressive symptoms in PLHIV. Mental health problems should be considered an integral part of adherence counselling. Our findings contribute to the available knowledge on risk factors for adverse outcomes of ART and may contribute to the ongoing development of healthcare policies currently being introduced in South Africa, such as National Health Insurance and the new 2030 Human Resources for Health Strategy. We believe that the use of our study results to strengthen adherence intervention strategies will subsequently improve health outcomes and decrease the number of patients switching to complex treatment options such as second-line and third-line ART regimens.

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SUMMARY

South Africa contributes about 20% (4.8 million) of the global number of HIV-positive people accessing antiretroviral therapy (ART). In 2019, an estimated 15%-20% of people on first-line ART and up to 30% of people on second-line ART in the South African HIV treatment program experienced virological failure. Further, up to approximately 40% of people on first-line ART and up to 20% of people on second-line ART were lost to follow-up (LTFU). Although there is much research on adherence to ART, there remains a dearth of studies relating to the multi-level factors associated with adherence to treatment and processes shaping adherence behaviour, particularly in South Africa. In addition, there is a lack of reported knowledge about the effectiveness and impact of strategies currently employed to promote adherence in people living with HIV (PLHIV) who are taking ART. In this thesis, a multilevel socio-ecological framework was used to provide information about risk factors affecting treatment adherence at different levels and also guided a systematic review of research assessing the impact or effects of intervention strategies in improving treatment adherence.

The studies presented in this thesis identified the barriers to and facilitators of adherence for people living with HIV on ART and assessed the impact of different adherence intervention strategies that aimed to promote treatment adherence. This was achieved by examining the five research questions:

1. What is the uptake rate of ART, and the individual-level predictors of virological failure and being lost to follow-up (LTFU) in PLHIV taking ART in urban communities?
2. What are the individual-level factors that predict virological failure, low CD4 count, and retention in care for patients on second-line ART in urban communities?
3. What are the individual, relationship or interpersonal, and community-level factors associated with self-reported adherence, pill count, and virological failure to ART in rural communities?
4. What are the different treatment-taking behaviours and perspectives on adherence to ART between virally suppressed and unsuppressed patients on second-line ART in urban communities?
5. What treatment adherence strategies and interventions have been implemented and evaluated in sub-Saharan Africa for ART, hypertension, and Diabetes Mellitus?

Chapter 2, a protocol paper, detailed the rationale, study aims, research designs, and methods employed in the studies reported on in this thesis. By adapting a multi-level socio-ecological framework to identify factors existing at various levels (including individual, relationship/interpersonal, and community level factors) and describing their interplay chapter 2 demonstrated how an existing socio-ecological conceptual framework can be used as a tool to provide guidance regarding facilitators and barriers to ART adherence.

In the study reported in chapter 3, we described the ART uptake and the individual level predictors of virological failure and being LTFU in PLHIV taking ART in Johannesburg. In this

retrospective cohort study, we presented analyses based on the TIER.Net database for a large cohort of HIV-infected adult patients who are taking first-line and second-line ART in Johannesburg, South Africa. TIER.Net is the ART monitoring and evaluation system used by the South African National Department of Health for recording ART patient-level information. Records were reviewed for patients on ART from seven high-volume public health facilities in Johannesburg. Study data included medical records of people with HIV who started ART between 01 April 2004 (the inception of the South African national HIV treatment program in the public health system setting) and 29 February 2020. This cut-off period was chosen to give the cohort patients a minimum of one year to receive their annual standard-of-care viral load test. In this study, factors such as age at ART start, current age, sex, duration on ART, baseline CD4 cell count, and retention in care were analyzed as covariates of outcomes (viral load and LTFU).

Of the total study cohort, 95% (n=117 260/123 002) were on a first-line regimen and 5% (n=5 742/123 002) were on a second-line regimen. Most patients (59%, n=72 430/123 002) were initiated on an efavirenz-based, tenofovir disoproxil fumarate-based and emtricitabine-based regimen (fixed-dose combination). 91% (n=76 737/84 252) achieved viral suppression at least once since initiating ART and 59% (n=57 981/98 071) remained in care as at the end of February 2020. Findings from the univariate, multivariable logistic regression analysis and fixed effect model showed that younger patients, male patients, patients with low CD4 cell counts, and patients who were initiated on ART between 2004 and 2010 all had poorer clinical, treatment and retention outcomes, particularly those on second-line ART. While national ART guidelines and efforts to initiate PLHIV on treatment have contributed to a higher uptake of ART over time, much still needs to be done to improve retention in care. Although slight efforts have been made to address similar findings in sub-Saharan Africa, these demographic and clinical characteristics must be considered when designing/implementing treatment support strategies and models to improve treatment outcomes, retention in care, and subsequently treatment failures which lead to switching to more complex ART regimens.

In the study reported in chapter 4, we aimed to identify individual-level factors that predict virological failure, low CD4 count, and retention in care for patients on second-line ART in Johannesburg. In this retrospective cohort study, we conducted analyses of secondary data that was exported from the TIER.Net database. Variables extracted included ART start dates, ART switch dates, treatment retention, viral load, and CD4 cell count results. This retrospective study of 825 PLHIV on second-line ART reported viral load suppression of 83% (n=570/686) among patients on second-line ART, demonstrating lower suppression rates compared to historic first-line treatment (92% suppression rate) in Johannesburg. Just under three-quarters (72%, n=597/825) of the patients remained in care over the reported period, slightly lower than the reported retention rate of 78% in a first-line treatment cohort from Johannesburg. Results from the multivariable logistic regression analysis reported that being <25 years of age, male sex, and geographical transfer (started initial treatment in a different region)

independently predicted low CD4+ cell counts and virological failure on second-line treatment. Being younger than 25 years of age, male sex, and transferred-in patients, are easily identifiable factors that may trigger the need for added adherence and support interventions, which include targeted adherence and retention support programs, using mobile health solutions for patient communication, education, and appointment reminders.

The study presented in chapter 5 investigated individual, relationship or interpersonal, and community-level factors associated with self-reported adherence, pill count, and virological failure to ART of patients accessing care at the Ndlovu Medical Centre, Limpopo Province. This study was performed as a sub-study of the Intensified Treatment Monitoring Strategy to Prevent Accumulation of Drug Resistance (ITREMA) randomized clinical trial, a well-characterized cohort of 501 participants on antiretroviral treatment, that received prospective long-term follow-up for 96 weeks. In this study, markers of adherence and virological suppression status were periodically assessed. A comprehensive assessment of multilevel risk factors at the baseline of this trial enabled us to characterize their association with study outcomes (viral load, self-reported adherence, and pill count). The multilevel factors included demographic information, employment status, income composition, household composition, partnership status, food security, adherence, actual support from household members, actual family support, coping abilities, clinician trust, health literacy, mental health, and stigmatization.

We found that over half (53%, n=243/458)) of the participants reported difficulties with adherence, and over one-third (35%, n=162/458) had suboptimal adherence measured through pill count (pill count<95%) at any point during follow-up. Virological failure appeared infrequently and occurred in 16% (n=68/436) of participants. Using tests of association and multivariable logistic regression analysis (stratified by sex), we found that being male was an independent risk factor for self-reported difficulties with adherence, suboptimal adherence measured through pill count, and virological failure. PLHIV who experienced moderate or severe depressive symptoms or had low household income were at increased risk of poor adherence and/or virological failure and may benefit from additional ART adherence support. In the stratified analysis, we found that the risk of virological failure was higher among male participants with food insecurity. We also found that while the prevalence of depressive symptoms was similar between males and females, the association was significant among female participants only. Task-oriented coping was associated with suboptimal adherence as indicated by pill count<95%. Our findings reported in chapter 5 contribute to the available knowledge on risk factors for adverse outcomes of ART in rural populations. The study findings may also contribute to the ongoing development of 'rural proof' healthcare policies currently being introduced in South Africa, such as the National Health Insurance and the new 2030 Human Resources for Health Strategy. These strategies seek to promote comprehensive access to healthcare services and also highlight the need for the government to take decisive steps to improve access to care for all individuals seeking healthcare services.

Chapter 6 reports a cross-sectional study that sought to describe the different treatment-taking behaviours and perspectives of adherence to ART between virally suppressed and unsuppressed patients using second-line ART in Johannesburg. This study was conducted between July 2018 and August 2018, in five public health facilities (two hospitals, one community health center, and two primary healthcare clinics). We randomly sampled 10% of the population of 1 500 eligible patients and they were invited to participate in this study in one of two ways; telephonically or in facility recruitment where researchers met them at the facility during their scheduled clinic visit.

The study sample comprised 149 participants; of which 48% (n=71/149) were virally unsuppressed. The majority of participants (63%, n=94/149) had disclosed their HIV status to their relatives and/or partners within one week of diagnosis. However, 28% (n=42/149) took longer than four weeks to disclose to their relatives and/or partners. Using multivariable logistic regression analysis, we found that single and unmarried people living with their partners were more likely to experience virological failure compared to those who were married. The more toxic second-line multi-pill, which is taken multiple times a day, was seen as significantly harder to take than a single tablet daily, well-tolerated first-line regimen. Participants experiencing medication-related difficulties in taking second-line ART and experiencing side effects were also subjective predictors of virological failure. We also found that participants with virological failure were more likely to have treatment-related side effects. Those participants with side effects were more likely to be unemployed. In general, employed individuals are linked to improved access to healthcare and better health outcomes as compared to their unemployed counterparts. However, while the correlation between improved health outcomes and employment exists, the causal relationship is complicated as the relationship can be bi-directional. Our study results suggest the importance of improving patients' knowledge about treatment and adherence, and motivation to continue ART use despite the persistence of side effects.

Participants interviewed in the study reported in chapter 6 had firm recommendations around improving adherence to second-line ART, largely focused on reduced dosing and pill burden. These included a second-line fixed-dose combination, a dosage taken once a day, and a reduction in the pill size. Furthermore, the participants suggested that education on the benefits of taking ART could improve adherence, whilst a few participants also suggested the implementation of injectable second-line ART.

In chapter 7, we report a systematic review that assessed the impact of interventions that aimed to promote adherence to treatment for chronic conditions (ART, hypertension, diabetes mellitus). We systematically searched the PubMed, Web of Science, Scopus, Google Scholar, and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases to identify relevant publications. Data were extracted from eligible studies for study characteristics and

description of interventions for the study populations of interest. We found a relatively large body of evidence on interventions to improve adherence among adults living with chronic conditions in sub-Saharan Africa. Of the 25 473 total studies/records screened, a total of 77 studies were subsequently included, describing a total of 49,364 patients. Of the total included studies, 70% (n=54/77) were related to ART for HIV, 8% (n=6) were anti-hypertensive medication related, 16% (n=12/77) were anti-diabetic medication related and 6% (n=5/77) focused on medication for more than one condition. Of the total 77 studies, 60% (n=46/77) reported improved adherence based on the described study outcomes while 21% (n=16/77) reported no significant difference between studied groups. There is expanded evidence that community-and home-based, digital, or mobile health (mhealth) and adherence counselling interventions can improve adherence to treatment for chronic conditions. Our findings underscore the need to develop a gold standard (or uniform measures) for measuring adherence.

In the general discussion in chapter 8, the main findings were summarized, collated, and discussed. Chapter 8 provided context to the findings about the research questions and discussed its implications for future research along with recommendations. Thereafter, the strengths, limitations of this thesis, and directions for future research were also discussed.

Combining multi-level models, the evidence from the studies presented in this thesis enabled us to identify the barriers to and facilitators of adherence for PLHIV on first-line and second-line ART and make recommendations for comprehensive, acceptable, and appropriate intervention strategies to improve treatment adherence. Our research found that many factors influence the ability to successfully engage individuals in HIV care. These factors include being male, being younger, experiencing ART-related side effects, having a low household income, presence of food insecurity, and experiencing moderate or severe depressive symptoms. With a large total sample size of 173 842 people included across all studies, our research ensured that a strong body of evidence was created regarding barriers to and facilitators of adherence to ART and adherence intervention strategies implemented to improve treatment adherence. However, all the research studies included in this thesis were conducted in a total of eight health facilities (seven of over 120 health facilities in one South African metropolitan municipality (urban setting) and one facility in a rural setting). While this ensured that study participants had comparable demographic profiles throughout the different studies in this thesis, these findings may not be generalizable to other regions or municipalities in South Africa, or other country settings. Nonetheless, studies reported in this thesis consisted of adequate study sample sizes to strengthen the effects of the findings. In addition, the direction and size of effect were generally consistent across all chapters, suggesting that the study findings may be robust despite limitations related to study settings. We believe that the use of our study results to strengthen adherence intervention strategies will subsequently improve health outcomes and decrease the number of patients switching to complex treatment options such as second-line and third-line ART regimens.

SAMENVATTING

Zuid-Afrika draagt ongeveer 20% (4,8 miljoen mensen) bij aan het wereldwijde aantal hiv-positieve mensen dat toegang heeft tot antiretrovirale therapie (ART). In 2019 ervoer naar schatting 15%-20% van de mensen op eerstelijns ART en tot 30% van de mensen op tweedelijns ART in het Zuid-Afrikaanse hiv-behandelprogramma virologisch falen. Bovendien raakte tot ongeveer 40% van de mensen op eerstelijns ART en tot 20% van de mensen op tweedelijns ART uit zicht van behandelaars (loss-to-follow-up; LTFU). Hoewel er veel onderzoek is gedaan naar de therapietrouw aan ART, ontbreekt het nog steeds aan studies naar de factoren op verschillende sociaalecologische niveau's die verband houden met therapietrouw en de geralteerde processen die therapietrouwgedrag beïnvloeden, met name in Zuid-Afrika. Daarnaast ontbreekt er beschreven kennis over de effectiviteit en impact van momenteel toegepaste strategieën om therapietrouw te bevorderen bij mensen met hiv (PLHIV) die ART gebruiken. In dit proefschrift is een multilevel sociaalecologisch raamwerk gebruikt om informatie te verkrijgen over risicofactoren die therapietrouw op verschillende niveaus beïnvloeden, en het stuurde ook een systematische review van onderzoek naar de effecten van interventiestrategieën om therapietrouw te verbeteren.

De studies in dit proefschrift geven inzicht in de factoren die therapietrouw van mensen met hiv aan ART belemmeren of bevorderen en analyseren het effect van verschillende interventiestrategieën gericht op het bevorderen van therapietrouw aan de hand van vijf onderzoeksvragen:

1. Wat is het percentage mensen met hiv dat ART gebruikt en wat zijn voorspellers op individueel niveau van virologisch falen en LTFU onder mensen met hiv die ART gebruiken in een stedelijke gemeenschappen?
2. Wat zijn de individuele factoren die virologisch falen, een laag CD4-aantal en behoud in zorg voorspellen van patiënten op tweedelijns ART in stedelijke gemeenschappen?
3. Wat zijn de factoren op individueel, relationeel of interpersoonlijk en gemeenschapsniveau die samenhangen met zelfgerapporteerde therapietrouw, pillentelling en virologisch falen bij ART in rurale gemeenschappen?
4. Wat zijn verschillen in behandelingsgerelateerde gedragingen en perspectieven op therapietrouw aan ART tussen viraal onderdrukte en niet-onderdrukte patiënten op tweedelijns ART in stedelijke gemeenschappen?
5. Welke strategieën en interventies om therapietrouw te bevorderen zijn in Sub-Sahara Afrika geïmplementeerd en geëvalueerd voor ART, hypertensie en diabetes mellitus?

Hoofdstuk 2, een protocolpaper, beschreef de achtergrond en doelstellingen van het onderzoek, de onderzoeksopzetten en de gebruikte methoden van de in dit proefschrift gerapporteerde studies. Aan de hand van een multi-level sociaalecologisch raamwerk om factoren op verschillende niveaus te identificeren (inclusief op individuele, relationeel of interpersoonlijk en gemeenschapsniveau) en hun onderlinge samenhang te beschrijven, liet hoofdstuk 2 zien hoe een bestaand sociaalecologisch conceptueel kader als instrument kan

worden gebruikt om inzichten te geven ten aanzien bevorderende en belemmerende factoren voor ART-therapietrouw.

In het onderzoek gerapporteerd in hoofdstuk 3 beschreven we de mate van ART-gebruik en de voorspellers op individueel niveau van virologisch falen en LTFU bij mensen met hiv die ART gebruiken in Johannesburg. In deze retrospectieve cohortstudie presenteerden we analyses op basis van de TIER.Net-database voor een grote cohort van volwassen hiv-geïnfecteerde patiënten die eerstelijns en tweedelijns ART gebruikten in Johannesburg, Zuid-Afrika. TIER.Net is het ART-monitoring- en evaluatiesysteem dat wordt gebruikt door het Zuid-Afrikaanse nationale ministerie van volksgezondheid voor het registreren van informatie over ART-gebruik op patiëntniveau. Dossiers van patiënten op ART van zeven drukke openbare gezondheidsinstellingen in Johannesburg werden beoordeeld. Studiegegevens zijn gebaseerd op de medische dossiers van mensen met hiv die tussen 1 april 2004 (het begin van het Zuid-Afrikaanse nationale publieke HIV-behandelingsprogramma) en 29 februari 2020 met ART begonnen. De einddatum voor inclusie is zodanig gekozen dat patiënten minimaal één jaar de tijd hadden om hun jaarlijkse standaard virale ladingtest te ontvangen. In deze studie werden factoren zoals leeftijd bij aanvang van ART, huidige leeftijd, geslacht, duur van ART, CD4-celtelling bij aanvang, en behoud in zorg geanalyseerd als covariaten van de uitkomsten (virale lading en LTFU).

Van het totale aantal patiënten in de studiecohort was 95% (n=117 260/123 002) op een eerstelijns regime en 5% (n=5 742/123 002) op een tweedelijns regime. De meeste patiënten (59%, n=72 430/123 002) waren geïnitieerd op een regime bestaande uit efavirenz, tenofovir disoproxil fumaraat en emtricitabine (vaste-dosiscombinatie). Van alle patiënten in het cohort bereikte 91% (n=76 737/84 252) ten minste eenmaal virale onderdrukking sinds de start van ART en 59% (n=57 981/98 071) bleef in zorg tot eind februari 2020. Bevindingen van de univariate en multivariate logistische regressieanalyses en het fixed effects-model toonden aan dat jongere patiënten, mannelijke patiënten, patiënten met een lager CD4-cel aantal en patiënten die tussen 2004 en 2010 met ART begonnen allemaal slechtere klinische, behandelings- en retentieresultaten hadden, vooral patiënten op tweedelijns ART. Hoewel nationale ART-richtlijnen en inspanningen om mensen met hiv te laten starten met ART hebben bijgedragen aan een grotere acceptatie van ART in de loop der tijd, moet er nog veel worden gedaan om behoud in zorg te verbeteren. Ondanks dat er al enige inspanningen zijn geleverd om soortgelijke situaties in Sub-Sahara Afrika aan te pakken die als voorbeeld kunnen dienen, moeten de specifieke demografische en klinische kenmerken van mensen met hiv in Zuid-Afrika die samenhangen met virale lading en behoud in zorg in acht worden genomen bij het ontwerpen en implementeren van strategieën en interventies voor behandelingsondersteuning om de behandelingsresultaten en behoud in zorg te verbeteren en uiteindelijk te voorkomen dat behandeling mislukt, wat noodzaakt tot overstappen op complexere ART-regimes te verbeteren.

In de in hoofdstuk 4 gerapporteerde studie wilden we factoren op individueel niveau identificeren die virologisch falen, een laag CD4-aantal en behoud in zorg voorspellen bij patiënten op tweedelijns ART in Johannesburg. In deze retrospectieve cohortstudie voerden we analyseert uit op secundaire gegevens die waren geëxporteerd uit de TIER.Net-database. Geëxtraheerde variabelen omvatten ART-startdatum, ART-wisseldatum, behoud in zorg, virale lading en CD4-aantal. Deze retrospectieve studie van 825 mensen met hiv op tweedelijns ART vond virale onderdrukking bij 83% (n=570/686) van de patiënten op tweedelijns ART, wat een lager onderdrukkingspercentage is vergeleken met historische gegevens voor eerstelijnsbehandeling in Johannesburg (92%). Iets minder dan driekwart (72%, n=597/825) van de patiënten bleef in zorg gedurende de onderzoeksperiode, iets lager dan het gerapporteerde retentiepercentage van 78% in een eerstelijnsbehandelingscohort in Johannesburg. Resultaten van de multivariate logistische regressieanalyse lieten zien dat jonger zijn dan 25 jaar, mannelijk geslacht en geografische overdracht (begonnen met initiële behandeling in een ander gebied) onafhankelijk samenhingen met een laag CD4-aantal en virologisch falen bij tweedelijns behandeling. Jonger zijn dan 25 jaar, mannelijk geslacht en geografische overdracht van behandeling zijn eenvoudig identificeerbare factoren die de behoefte aan extra therapietrouw en ondersteunende interventies kunnen indiceren, waaronder gerichte interventie- en ondersteuningsprogramma's, en het gebruik van mobiele gezondheidsoplossingen voor patiëntcommunicatie, educatie en afspraakherinneringen.

Het onderzoek gepresenteerd in hoofdstuk 5 onderzocht factoren op individueel, relationeel of interpersoonlijk en gemeenschapsniveau die geassocieerd zijn met zelfgerapporteerde therapietrouw, pillentelling en virologisch falen bij mensen met hiv die ART gebruiken en zorg krijgen bij het Ndlovu Medical Centre in de provincie Limpopo. Deze studie werd uitgevoerd als sub-studie van de Intensified Treatment Monitoring Strategy to Prevent Accumulation of Drug Resistance (ITREMA) gerandomiseerde klinische trial, in een goed gekarakteriseerd cohort van 501 deelnemers die ART gebruikten en die prospectief en gedurende 96 weken opgevolgd werden. In deze studie zijn indicatoren van therapietrouw en virale onderdrukking periodiek bekeken. Een uitgebreide analyse van informatie over multilevel risicofactoren die aan het begin van dit onderzoek is verkregen stelde ons in staat om samanhangen met de onderszoeksuitkomsten (virale lading, zelfgerapporteerde therapietrouw en pillentelling) te analyseren. De multilevel factoren omvatten demografische informatie, informatie over werk en inkomen, relatie status, samenstelling huishouden, voedselzekerheid, therapietrouw, ondersteuning van leden van het huishouden, ondersteuning van familie, coping, vertrouwen in zorgverleners, gezondheidsvaardigheden, mentale gezondheid, en ervaren stigmatisering.

We vonden dat meer dan de helft (53%, n=243/458) van de deelnemers moeilijkheden meldde met therapietrouw en dat meer dan een derde (35%, n=162/458) suboptimale therapietrouw ervoer op enig moment tijdens de follow-up, gemeten aan de hand van pillentelling (pillentelling <95%). Virologisch falen kwam zelden voor en trad op bij 16% (n=68/436) van de deelnemers. Aan de hand van correlatie analyses en multivariate logistische regressieanalyse

(gestratificeerd naar geslacht) vonden we dat mannelijk geslacht een onafhankelijke risicofactor was voor zelfgerapporteerde moeilijkheden met therapietrouw, suboptimale therapietrouw gemeten aan de hand van pillentelling, en virologisch falen. Mensen met hiv die matige of ernstige depressiesymptomen ervoeren of een laag huishoudinkomen hadden, liepen een ook verhoogd risico op suboptimale therapietrouw en/of virologisch falen en zouden eveneens baat kunnen hebben bij aanvullende ondersteuning bij ART. In de gestratificeerde analyse vonden we dat het risico op virologisch falen hoger was bij mannelijke deelnemers met voedselonzekerheid. We vonden ook dat, hoewel de prevalentie van depressieve symptomen vergelijkbaar was tussen mannen en vrouwen, de samenhang alleen significant was bij vrouwelijke deelnemers. Probleemgerichte coping hing samen met suboptimale naleving therapietrouw gebaseerd op een pillentelling <95%. Onze bevindingen in Hoofdstuk 5 dragen bij aan de beschikbare kennis over risicofactoren voor suboptimale uitkomsten van ART in rurale populaties. De onderzoeksresultaten kunnen ook bijdragen aan de ontwikkeling van gezondheidsbeleid dat ook geschikt is voor rurale gebieden dat momenteel wordt geïntroduceerd in Zuid-Afrika, zoals de Nationale Gezondheidsverzekering en de nieuwe Human Resources for Health Strategy 2030. Deze strategieën streven naar brede toegang tot gezondheidsdiensten en benadrukken ook de noodzaak voor de overheid om beslissende stappen te zetten om de toegang tot zorg te verbeteren voor alle personen die gezondheidsdiensten zoeken.

Hoofdstuk 6 rapporteert een dwarsdoorsnedeonderzoek dat verschillen in gedragingen en perspectieven op bevordering van therapietrouw aan ART beschrijft tussen mensen met hiv in Johannesburg die tweedelijns ART gebruiken en bij wie het virus viraal onderdrukt of niet-onderdrukt is. Dit onderzoek werd uitgevoerd tussen juli 2018 en augustus 2018, in vijf publieke gezondheidsinstelling (twee ziekenhuizen, een gezondheidscentrum en twee eerstelijnsgezondheidsklinieken). We includeerden willekeurig een steekproef van 10% van de populatie van 1500 patiënten die in aanmerking kwamen en nodigden hen op een van twee manieren uit om deel te nemen aan dit onderzoek: telefonisch of door werving in de instelling waar onderzoekers contact met hen hadden rondom een gepland kliniekbezoek. De onderzoekspopulatie bestond uit 149 deelnemers, waarvan 48% (n=71/149) viraal niet-onderdrukt was. De meerderheid van de deelnemers (63%, n=94/149) had hun hiv-status binnen één week na diagnose aan hun familieleden en/of partner bekendgemaakt. Echter, 28% (n=42/149) deed er langer dan vier weken over om het aan hun familieleden en/of partner te vertellen.

Met behulp van multivariate logistische regressieanalyse vonden we dat alleenstaande mensen en ongetrouwde mensen die samenwoonden met hun partners meer kans hadden op virologisch falen in vergelijking met degenen die getrouwd waren. De meer toxische tweedelijns combinatiepil, die meerdere keren per dag ingenomen moet worden, werd beschouwd als aanzienlijk moeilijker in te nemen dan een enkele tablet per dag in een goed verdragen eerstelijnsregime. Het ervaren van problemen met het innemen van tweedelijns

ART en het ondervinden van bijwerkingen waren ook subjectieve voorspellers van virologisch falen. We vonden ook dat deelnemers met virologisch falen meer kans hadden op behandeling-gerelateerde bijwerkingen. Deelnemers met bijwerkingen hadden ook meer kans om werkloos te zijn. Over het algemeen hebben werkende individuen betere toegang tot gezondheidszorg en betere gezondheidsresultaten in vergelijking met hun werkloze tegenhangers. De causale relatie tussen werken en betere gezondheidsresultaten is gecompliceerd omdat de invloed in beide richtingen kan zijn. Onze onderzoeksresultaten onderstrepen het belang van het verbeteren van de kennis van patiënten over behandeling en therapietrouw, en van de motivatie om tweedelijns ART-gebruik vol te houden ondanks (aanhoudende) bijwerkingen. De deelnemers hadden ook duidelijke aanbevelingen om de therapietrouw aan tweedelijns ART te bevorderen, vooral gericht op verminderde dosering en pilbelasting. Deze aanbevelingen waren om te komen tot een vaste combinatie van middelen, een dosering die eens per dag wordt ingenomen en het verkleinen van de pilgrootte. Bovendien suggereerden de deelnemers dat voorlichting over de voordelen van het innemen van ART de therapietrouw zou kunnen verbeteren. Enkele deelnemers suggereerden ook de implementatie van injecteerbare tweedelijns ART.

In hoofdstuk 7 rapporteerden we een systematische review naar de impact van interventies om therapietrouw aan behandeling voor chronische aandoeningen te bevorderen (ART, hypertensie, en diabetes mellitus). Voor deze systematische review is systematisch gezocht in PubMed, Web of Science, Scopus, Cumulative Index of Nursing and Allied Health Literature (CINAHL) en Google Scholar om relevante publicaties te identificeren. Van de aanmerking komende studies is informatie geëxtraheerd over de kenmerken van het onderzoek en de beschrijving van de interventies voor de relevante onderzoekspopulaties. We vonden een relatief grote hoeveelheid ondersteunend bewijs voor interventies om therapietrouw te bevorderen bij volwassenen die leven met chronische aandoeningen in Sub-Sahara Afrika. Van de in totaal 25,473 verwijzingen naar publicaties die zijn bekeken, werden uiteindelijk 77 publicaties geïncludeerd in de systematische, die betrekking hadden op onderzoek met in totaal 49.364 patiënten. Van het totaal aantal geïncludeerde studies was 70% (n=54/77) gerelateerd aan ART voor hiv, 8% (n=6) was gerelateerd aan anti-hypertensie medicatie, 16% (n=12/77) was gerelateerd aan diabetes medicatie en 6% (n=5/77) richtte zich op medicatie voor meer dan één aandoening. Van de 77 studies vond 60% (n=46/77) betere therapietrouw op basis van de beschreven onderzoeksresultaten, terwijl 21% (n=16/77) geen significant verschil rapporteerde tussen de bestudeerde onderzoekscondities. Er is veel bewijs dat interventies in de gemeenschap- of middels huisbezoek, digitale of mobiele gezondheids- (mhealth) interventies en counseling-interventies de therapietrouw aan behandelingen voor chronische aandoeningen kunnen verbeteren. Onze bevindingen onderstrepen de noodzaak om een gouden standaard (of uniforme instrumenten) te ontwikkelen voor het meten van therapietrouw.

In de algemene discussie in hoofdstuk 8 zijn de belangrijkste bevindingen samengevat, geordend en besproken. Hoofdstuk 8 gaf context aan de bevindingen in relatie tot de onderzoeksvragen, ging in op de implicaties voor toekomstig onderzoek, en beschreef aanbevelingen. Vervolgens werden ook de sterke punten en beperkingen van het onderzoek in dit proefschrift besproken, evenals mogelijkheden voor toekomstig onderzoek om de beperkingen van het huidige onderzoek aan te pakken. Door het gebruik van multi-level modellen konden we, op basis van de resultaten van de studies die in dit proefschrift zijn gepresenteerd, belemmerende en bevorderende factoren voor therapietrouw van mensen met hiv aan eerste- en tweedelijns ART identificeren. Op basis van deze bevindingen zijn aanbevelingen gedaan voor omvattende, aanvaardbare en passende interventiestrategieën om therapietrouw aan behandeling te bevorderen. Ons onderzoek liet zien dat diverse factoren van invloed zijn op het succes van hiv-zorg. Factoren die samenhangen met minder behandelingssucces omvatten mannelijk geslacht, jongere leeftijd, het ervaren van ART-gerelateerde bijwerkingen, een laag huishoudinkomen, voedselonzekerheid en het ervaren van matige of ernstige symptomen van depressie. Met een totale steekproefgrootte van 173 842 mensen in alle studies samen, draagt het onderzoek in dit proefschrift bij aan sterk bewijs met betrekking tot bevorderende en belemmerende factoren van therapietrouw aan ART. Het onderzoek in dit proefschrift draagt ook bij aan bewijs voor interventiestrategieën om therapietrouw aan ART te bevorderen.

Alle onderzoeken met mensen met hiv die in dit proefschrift beschreven zijn, werden uitgevoerd in een of meer van slechts acht gezondheidsinstellingen, waaronder zeven van de meer dan 120 gezondheidsinstellingen in het grootste stedelijke gebied in Zuid-Afrika en één instelling in een landelijke omgeving. Hoewel de focus op specifieke gezondheidsinstellingen eraan bijdroeg dat deelnemers uit stedelijk gebied in de verschillende studies vergelijkbare demografische profielen hadden, zijn de bevindingen daardoor echter niet generaliseerbaar naar andere delen van Zuid-Afrika, of naar andere landen. Desalniettemin zijn de studies die gerapporteerd werden in dit proefschrift uitgevoerd met voldoende grote steekproeven, hetgeen het vertrouwen in de bevindingen versterkt. Bovendien waren de richting en grootte van samenhangen over het algemeen consistent in de verschillende studies, wat suggereert dat de bevindingen van het onderzoek robuust zijn, ondanks beperkingen met betrekking tot de onderzoekssetting. Wij hopen dat het gebruik van de onderzoeksresultaten voor het versterken van interventiestrategieën om therapietrouw te bevorderen uiteindelijk zal bijdragen aan verbeterde gezondheidsuitkomsten en het aantal patiënten dat overschakelt naar meer complexe behandelingsopties, met name tweedelijns- en ook derdelijns ART-regimes, zal verminderen.

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CURRICULUM VITAE AND LIST OF PUBLICATIONS

Siphamandla Bonga Ziphozonke Gumede (born in KwaZulu Natal, South Africa in 1984) is a medical scientist with an interest in quantitative research (and related research methods), monitoring and evaluation (M&E), data management, and data analyses. His passion for research began in 2008 when he worked at Wits Reproductive Health and HIV Institute (Wits RHI) as a Data Manager, supporting the maternal health programme. At the time, he was involved in data management activities which included database development, data collection, data cleanup, and analysis.

Between 2010 and 2018, he worked as an M&E Specialist, providing related support to various projects within Wits RHI, the Department of Health, and Johannesburg Metro Municipality. During the formation of Ezintsha in 2018, Samanta Lalla-Edward and Celicia Serenata presented an opportunity for him to work on the ART optimization project where he would focus on describing the ART profile for people living with HIV (PLHIV), a project that was supervised by Samanta Lalla-Edward and Francois Venter. That project paved the way for his joint PhD project between Utrecht University (The Netherlands) and Wits University (South Africa), which started in 2019. The objective for his PhD was to strengthen the understanding of adherence strategies for PLHIV who are on ART in comparison with other chronic conditions, supervised by Samanta Lalla Edward (Ezintsha and Wits University, South Africa), John de Wit (Utrecht University, the Netherlands), Francois Venter (Ezintsha and Wits University, South Africa) and Annemarie Wensing (University Medical Center Utrecht, the Netherlands). Between 2019 and 2022, he mainly focused on his PhD activities but continued to provide M&E, data management, and research-related support to various projects within Ezintsha.

In 2022, he joined Ezintsha's iHEART-SA project which is evaluating the interventions for integrating hypertension care into HIV care. Using evidence-based interventions, such as care coordinators (primary health care nurses) and decision-support tools, iHEART-SA aims to strengthen the integration of chronic conditions within the public health setting. His activities in the iHEART-SA project include providing research related support, data management, M&E, technical support, and staff management.

In addition to his iHEART-SA-related activities, he provides supervision to postgraduate students, providing an opportunity for them to deepen and consolidate their learning, and to set new goals towards their academic journeys. He provides students with the training, research support, and mentoring they need to perform required tasks and provides regular feedback and coaching.

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