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Mobile text messaging intervention to improve antiretroviral treatment adherence among adolescents living with HIV in Ethiopia

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2024

Document Version:

Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for published version (APA):

Tanga, A. T. (2024). *Mobile text messaging intervention to improve antiretroviral treatment adherence among adolescents living with HIV in Ethiopia*. [Doctoral Thesis (compilation), Department of Health Sciences]. Lund University, Faculty of Medicine.

Total number of authors:

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Mobile text messaging intervention to improve antiretroviral treatment adherence among adolescents living with HIV in Ethiopia

Abayneh Tunje Tanga



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Faculty of Medicine

Department of Health Sciences

ISBN 1652-8220

ISSN 978-91-8021-521-3

Lund University, Faculty of Medicine Doctoral Dissertation Series 2024:28



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Abstract

Adherence to antiretroviral therapy is a global problem among adolescents living with human immunodeficiency viruses (HIV), and it is associated with treatment failure and the development of viral resistance. One of the most significant barriers to treatment adherence among adolescents is forgetting to take drugs as prescribed. One of the key strategies recommended to improve this problem is the use of mobile phone text message. However, it is not yet shown how effective these interventions are and how new technologies will be integrated into the routine care system. Therefore, the aim of this thesis was to develop, test the feasibility, and evaluate the effectiveness of mobile phone text messaging interventions in improving adherence to, and retention in, care among adolescents living with HIV in Southern Ethiopia. This thesis includes a systematic review and meta-analysis (Paper I), one qualitative study (Paper II), one convergent mixed-method study (Paper III), and a randomized controlled trial (Paper IV). In Paper I, there was inconclusive evidence that mobile text message reminders improved antiretroviral therapy (ART) adherence in adolescents. In Paper II, treatment adherence and retention in HIV care experiences, and the needs of adolescents living with HIV, were explored among 18 adolescents living with HIV in Southern Ethiopia. Among the identified barriers to adherence were forgetting medication or medication time, a lack of privacy, perceived stigma, and lack of support. In Paper III, a process evaluation was conducted among 153 adolescents assigned to the intervention arm, and the result showed that 99.4% of the 30,700 reminder messages sent were successfully delivered. The problems of the 0.6% failed messages were identified. A five-dimensions evaluation approach was used. In Paper IV, 306 adolescents randomly assigned to intervention and control arms were followed for six months. The result revealed that the average effect of proportion of adherence increased in the intervention arm, while viral load decreased. Therefore, the findings of this thesis provide promising evidence that automated mobile text message reminders improve adherence among patients living with HIV in resource-constrained settings.

Original papers

Paper I

Mehra N, Tunje A, Hallström IK, Jerene D. Effectiveness of mobile phone text message reminder interventions to improve adherence to ART among adolescents living with HIV: A systematic review and meta-analysis. *PLoS One*. 2021 Jul 22;16(7):e0254890. doi: 10.1371/journal.pone.0254890. PMID: 34293033; PMCID: PMC8297901

Paper II

Tunje A, Jerene D, Kristensson Hallström I. ART and retention in care experiences and Needs of Adolescents Living with HIV in Southern Ethiopia. *HIV AIDS (Auckl)*. 2021 Nov 26; 13:999–1007. doi: 10.2147/HIV.S339413. PMID: 34858061; PMCID: PMC8631828.

Paper III

Tunje A, Åvik Persson H, Jerene D, Kristensson Hallström I. Intervention fidelity and factors affecting the process of implementing a mobile phone text messaging intervention among adolescents living with HIV: a convergent mixed methods study in southern Ethiopia.

Paper IV

Tunje A, Kristensson Hallström I, Jerene D. Effectiveness of regular mobile text message reminders to improve adherence to antiretroviral treatment in adolescents living with HIV in Ethiopia: results from an individual randomized controlled trial.

Abbreviations

3TC	Lamivudine
ABC	Abacavir antiretroviral
ALHIV	Adolescents living with HIV
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Azidothymidine
CD4+	Type of T-lymphocyte, white blood cells
CONSORT	Consolidated standards of reporting trials
DTG	Dolutegravir
EFV	Efavirenz
ELISA	Enzyme-linked immunosorbent assay
HBM	Health belief model
HIV	Human immunodeficiency virus
HMIS	Health management information systems
INIs	Integrase inhibitors
INSTI	Integrase strand transfer inhibitor
LPV	Lopinavir
MRC	Medical research council
NEP+	Network of HIV positive in Ethiopia
NRTIs	Nucleoside reverse transcriptase inhibitors
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NVP	Nevirapine

PIs	Protease Inhibitors
RE-AIM	Reach effectiveness adoption implementation maintenance
RCT	Randomized Controlled Trial
RTV	Ritonavir
SDG	Sustainable Development Goal
SIV	Simian Immunodeficiency Virus
TLD	Dolutegravir
UNICEF	United Nations Children's Fund
WHO	World Health Organization
ZDV	Zidovudine (also abbreviated as AZT)

Introduction

Since the first cases were reported in 1981, nearly 86 million people have been infected with human immunodeficiency viruses (HIV), making it one of the world's most pressing health and development challenges (UNAIDS, 2023). Adolescents account for about 4% of all people living with HIV in the world. Although the last decade has seen a reduction in acquired immunodeficiency syndrome (AIDS)-related mortality worldwide, largely due to improved access to effective ART, AIDS remains a significant contributor to adolescent mortality in sub-Saharan Africa (Adejumo, Malee, Ryscavage, Hunter, & Taiwo, 2015). In addition, adolescents not receiving lifesaving ART can easily transmit a new infection to others. Globally, 140,000 adolescents aged 10 to 19 were newly infected with HIV in 2022 (UNICEF, 2023b).

Expansion and strengthening the provision of ART care and treatment across various levels, combined with focused social mobilization and engaged community involvement, aim to establish favorable conditions for curbing the epidemic's transmission. Currently, different partners are working together to meet the United Nations Sustainable Development Goal 3.3 (SDG 3.3) for ending the global AIDS epidemic as a public health issue by 2030, as well as to meet the UNAIDS 95-95-95 fast-track target (UNAIDS_Update, 2023).

Ethiopia is among the countries receiving external funding support to strengthen laboratory systems, supply chain management, and strategic information collecting, particularly health management information systems (HMIS) (PEPFAR, 2023). The Ethiopian government launched the Health Sector Transformation Plan (HSTP I-II), which was well designed to link to the National HIV Prevention Road Map, and to development partners' and non-governmental organizations' work (FMOH, 2018).

However, Ethiopia is unlikely to meet the first fast-track targets (UNAIDS, 2017). The mobilization of political leadership and identification of strategic and programmatic gaps in adolescent health and HIV responses have resulted in significant contributions to strategic information, national and district work planning, and the development and implementation of national policies.

Several factors influence the implementation of national policies to improve HIV treatment success among adolescents. Adolescents are more likely to experience

multiple and multifaceted challenges associated with physical, psychosocial, and cognitive development, and a contextual environment that is often stigmatizing (Adejumo et al., 2015).

As a result, other intervention packages are recommended in the national comprehensive HIV care implementation guideline to support treatment and care. Mobile phone text messages are considered to be one of the reminder tools for promoting adherence to ART as part of a package of adherence interventions (FMOH, 2018).

Closing the existing disparities in HIV diagnosis, treatment, and viral suppression is imperative to achieve epidemic control. Enhancing adherence among adolescents is crucial. Mobile text messaging has provided an opportunity for more structured, documented, and targeted interventions to be delivered for patient support and monitoring. Therefore, the purpose of this thesis was to develop, test the feasibility, and evaluate the effectiveness of mobile phone text messaging interventions in improving adherence to and retention in HIV care in specific facility among adolescents living with HIV in the south of Ethiopia.

Background

Epidemiology of HIV

HIV affects all regardless of skin color, gender, or socioeconomic status. An estimated 85.6 million people have been infected with the HIV since the epidemic, with 40.4 million deaths. However, differences in the number of new HIV infections between gender are more pronounced at younger ages, where new infection among young women was higher than they were among men in the same age group, with the burden of the pandemic varying greatly between countries and regions. In 2022, 39.0 million people were living with HIV worldwide. This comprises 37.5 million adults, 1.5 million children (under 15 years old) and 1.7 million adolescents. Among these, 1.3 million were new infections, and 630,000 died from AIDS globally. Women and girls (of all ages) accounted for 53% of all people living with HIV and 46% of all new HIV infections (WHO, 2022).

Many of the adolescents living with HIV today were infected with HIV as infants, and in the next decade millions of children living with HIV will transition into adolescence and adults. Adolescents account for about 4% of all people living with HIV and about 10% of new adult HIV infections. Of these, about 85% of adolescents live in sub-Saharan Africa (UNICEF, 2023a).

HIV has a disproportionate impact in certain regions of the world. The WHO African region is the most affected, with 25.6 million people living with HIV by 2022. This comprises 20.8 million people in eastern and southern Africa and 4.8 million in western and central Africa, while 3.9 million in South-East Asia, 3.8 million in the Americas, 3 million in Europe, 2.2 million in the Western Pacific, and 490 000 in the Eastern Mediterranean (UNAIDS/WHO, 2023) are also affected. Countries in East Africa have shown remarkable progress over the years in preventing and controlling the HIV/AIDS epidemic, yet still, they carry a high burden of HIV/AIDS in the world. According to the 2018 UNAIDS update, the burden of HIV/AIDS in the region has shown steady decline for the past 10 years (HIV/AIDS, 2018).

Ethiopia is one of the HIV high-burden countries, with an estimated 610,335 people living with HIV in 2018 (EPHI, March 2018). HIV or AIDS is said to have

started spreading rapidly in Ethiopia in the 1980s and 1990s along major transportation routes, primarily among commercial sex workers, truck drivers, and soldiers (Kibret et al., 2019).

The prevalence of HIV in adults (aged 15–49) reduced significantly from 1.8% in 1990 to 0.76% in 2022 (UNAIDS, 2022). However, the prevalence of HIV rose among adolescents and youth in Ethiopia, particularly in the younger age group (15–19). The prevalence is seven times higher in urban- than in rural areas (CSA, 2016; EPHI, August 2018b) and varies among regions, ranging from less than 0.17% in the Somali region to 4.8% in Gambella (FHAPCO, 2018).

Epidemiological research indicates that the majority of HIV cases in adolescents were acquired through mother-to-child transmission (during pregnancy, childbirth, or breastfeeding) and were sustained due to access to ART, enabling the adolescents' survival (Ferrand et al., 2010; Lowenthal et al., 2014).

However, the prospects and long-term journey for adolescents who contracted HIV at birth or through horizontal transmission are accompanied by specific disadvantages. These include the lifelong necessity for medication, the possible enduring negative impacts of antiretroviral drugs, and the stigma and discrimination associated with HIV infection. Equally, adolescents infected through horizontal transmission face similar challenges arising from exposure to HIV-contaminated blood products, unsterilized needles or medical equipment, and ingestion of HIV through breastmilk (Glaser, 2016).

Transmission

Research indicates that HIV is categorized into two types: HIV-1 and HIV-2, both believed to have originated from primate species like chimpanzees, gorillas, and sooty mangabeys (Hahn, Shaw, De, Cock, & Sharp, 2000). These are separate viruses with distinct genetic characteristics, both capable of causing AIDS and utilizing identical receptors and coreceptors to infect similar groups of cells (Motomura, Chen, & Hu, 2008).

The transmission of the virus from chimp to human is most likely to have occurred in humans in south-eastern Cameroon as a result of exposure to infected blood and other fluids while hunting and slaughtering for food (Hahn et al., 2000). Although both cause AIDS through the same route of transmission, the viruses differ significantly in terms of epidemiology, natural history, diagnosis, and management (Campbell-Yesufu & Gandhi, 2011).

HIV-1 infection is widespread throughout the world, with an estimated 40 million people infected (Wiktor et al., 1999). However, HIV-2 infection is most common in West African countries such as Guinea-Bissau, Gambia, Senegal, Cape Verde, Cote d'Ivoire, Mali, Sierra Leone, and Nigeria (CDC, 1988; Geoffrey S Gottlieb, Raugi, & Smith, 2018) (CDC, 1988). Although uncommon, HIV-2 infection is reported in many countries with cultural and socioeconomic ties to West Africa, including Europe, South America, Asia, and the United States.

Although HIV-1 and HIV-2 have similar basic gene arrangement, modes of transmission, intracellular replication pathways, and clinical outcomes, and both cause AIDS (Nyamweya et al., 2013), it is important to understand the transmission characteristics of each type (CDC, 2011). HIV-1 is transmitted through sexual intercourse, vertical transmission from mother to child, (Powers, Poole, Pettifor, & Cohen, 2008; Selik, Chu, & Ward, 1995), and horizontal transmission from the concomitant high frequency of genital ulcer diseases (such as syphilis), as well as the widespread use of unsterile injections (Cameron et al., 1989; Marx, Alcabas, & Drucker, 2001). People with HIV-infected sexual partners, children born to HIV-infected mothers and breast milk, intravenous drug users who share HIV-contaminated needles, and recipients of insufficiently screened blood products are the most vulnerable (Selik, Karon, & Ward, 1997).

HIV-2 is also transmitted by sexual, mother-to-child, and blood-borne pathways (G.S. Gottlieb, 2018). However, the pathogenic potential of HIV-2 is thought to be lower than that of HIV-1 (Kanki et al., 1994). Globally, an estimated 1–2 million people are infected with HIV-2. HIV-2 is less common due to a lowered plasma viral load, which is often undetectable (van der Loeff et al., 2010), resulting in a lower probability of horizontal and vertical transmission (Berry et al., 2002). In natural history perinatal studies conducted in West Africa, the rate of perinatal transmission of HIV-2 was significantly lower than for HIV-1, typically less than 5% versus approximately 25% (Adjorlolo-Johnson et al., 1994).

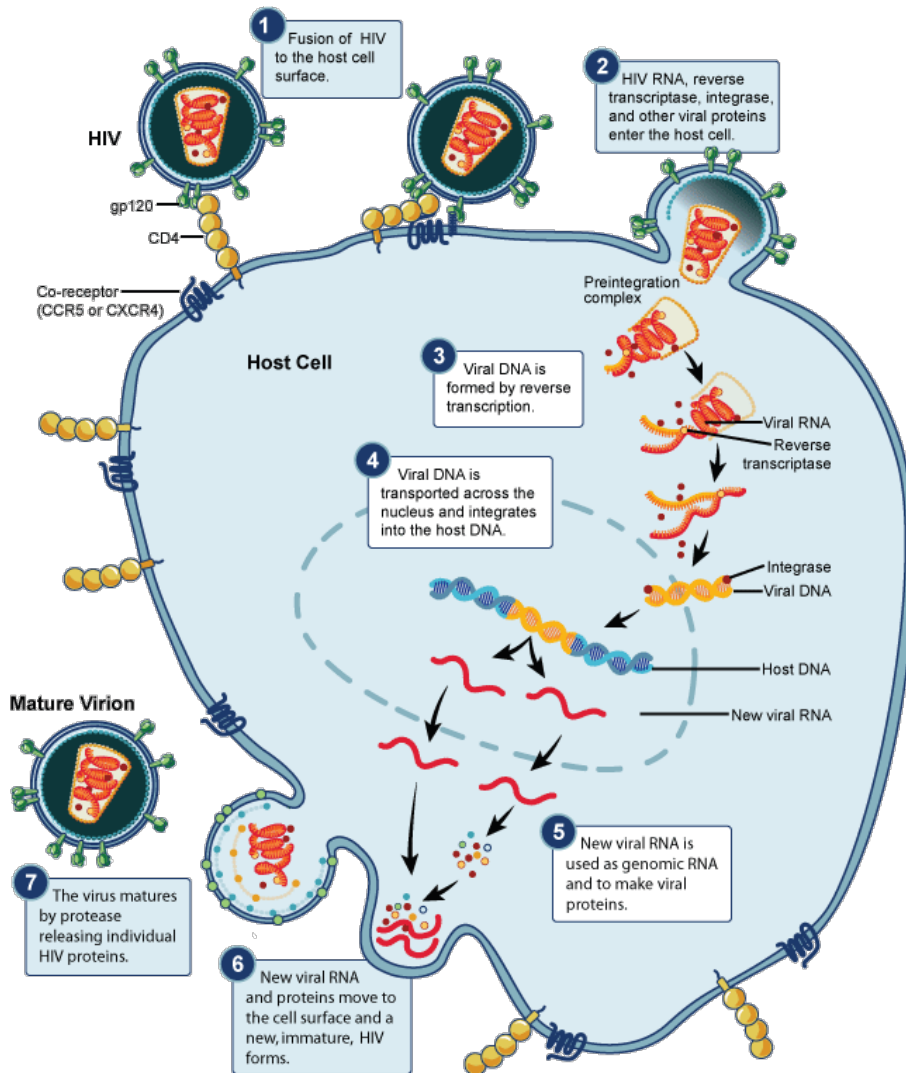
Pathogenesis

HIV pathogenesis has been shown to be complicated and dynamic. HIV replication occurs at a high level throughout infection and there is a highly dynamic interplay between the host immune response, attempts by the host to replace cells that are destroyed, and virus and viral evolution that appear to differ among various tissue compartments. The replication process is divided into stages. HIV must first contact a CD4 cell before infecting it. The proteins on the surface of HIV (gp41 and gp120)

then bind to receptors on the surface of CD4+ T cells (typically the CD4 receptor and the CCR5 coreceptor).

When HIV binds to a CD4 cell, the capsid is released into the cell's main body (called the cytoplasm). The capsid then reaches the nucleus of the cell, where it releases three important enzymes. These proteins are the proteins that HIV uses to replicate. The first enzyme is reverse transcriptase (RT), which converts HIV's single strand (called RNA) into a double strand compatible with human DNA. The new double-stranded HIV is now capable of being integrated into human DNA.

The CD4 nucleus then starts producing raw material for new HIV replication. These new HIV particle strands must be split and reassembled to form a new virus. Protease is an enzyme that helps in cutting and assembly processes. After that, the newly produced virus must leave the cell. The newly released viruses (known as virions) then infect more CD4 cells, and this process is repeated. Eventually, the old CD4+ T cells died. This continuous procedure occurs millions of times each day when not on ART (see Figure 1).



Courtesy: National Institute of Allergy and Infectious Diseases
www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle

Figure 1. HIV virus replication cycle.

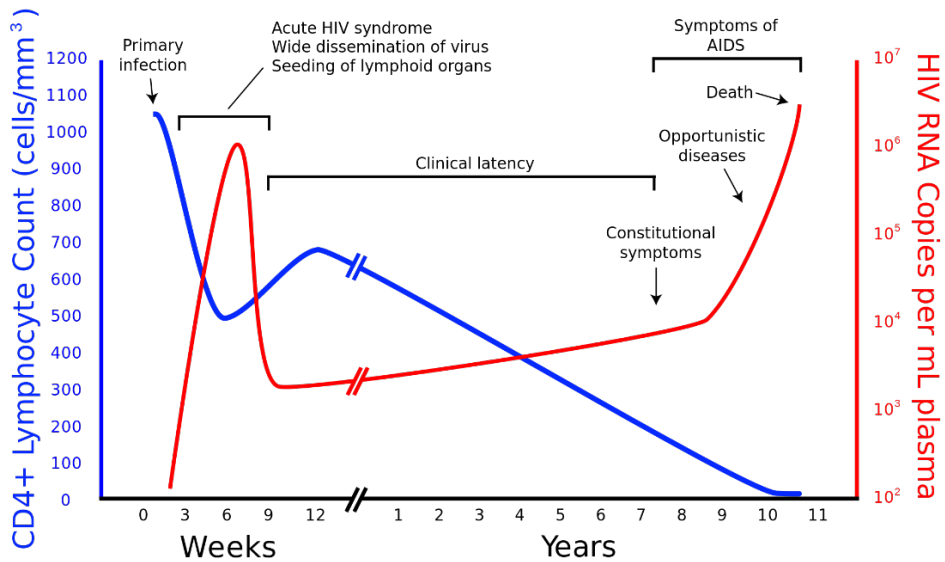
HIV infection has three phases. When HIV enters the body, it infects a significant number of CD4+ T cells and rapidly replicates. Infection with HIV occurs in three stages. During the acute phase of infection, the blood contains a large number of HIV copies (viral load), which spread throughout the body, seeding multiple organs,

particularly lymphoid organs such as the thymus, spleen, and lymph nodes. The virus may integrate and hide within the cell's genetic material at this stage.

Most people who become HIV infected experience an illness characterized often by fever, sore throat, lymphadenopathy, and rash (Schacker, Collier, Hughes, Shea, & Corey, 1996). These symptoms are frequently severe enough that people seek medical attention. However, during the first few weeks of infection, serum antibodies to HIV proteins are often insufficient to identify infection by enzyme-linked immunosorbent assay (ELISA) and immunoblotting, yet considerable amounts of HIV RNA can be found in plasma (Veazey et al., 1998). When symptoms go away, most people will remain symptom-free until a progressive depletion of CD4⁺ T cells from circulation and lymph nodes occurs, and their circulating CD4 T-cell count drops to 200 cells/L or lower (Mellors et al., 1996).

Acute infection has been identified as a risk factor for HIV transmission due to the high viral load associated with any risk behaviors. As a result, early detection and treatment will have a significant impact on HIV prevention and individual health outcomes (Brenner et al., 2007; Lundgren et al., 2015; Wawer et al., 2005).

After these symptoms disappear, the virus continues to spread, but at a low rate. This is the second phase of HIV infection, often known as chronic HIV infection. Patients at this phase may not have symptoms, but they can transmit the infection to others. AIDS is the most severe and last phase of HIV infection, and it is characterized by a high incidence of opportunistic infections (Lackner, Lederman, & Rodriguez, 2012). Figure 2.



Source: web site. https://commons.wikimedia.org/wiki/File:Hiv-timecourse_copy.svg

Figure 2. HIV copies and CD4 counts in a human over the course of a treatment-naive HIV infection.

Treatment

Medical treatment

Antiretroviral treatment (ART) is treatment of people infected with HIV using anti-HIV drugs. In individuals with advanced HIV disease, the use of certain antimicrobials for prevention and treatment of common opportunistic infections is also an essential part of the care package.

Researchers discovered that Zidovudine, a cancer medicine that failed in the 1960s, was used for HIV treatment in 1987 and was commercialized under the trade name Retrovir and azidothymidine (AZT), which has transformed HIV into a manageable chronic condition. This medicine, however, did not work well when used alone, and survival among infected patients who received this treatment was measured in weeks and months (Watson, 2022). Then, scientists subsequently discovered two new antiretroviral drugs, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), suggesting that combination antiretroviral treatment could stop the virus (Ho, 1995).

A combination of three or more antiretroviral medicines (cART) is more effective than using just one medicine (monotherapy) to treat HIV. However, these drugs do not kill or eliminate the virus when taken in combination; they can prevent multiplication of the virus, eliminate the virus circulating in the blood, and slow the progression of HIV (Table 1).

Table 1. Summary of sequencing options for preferred first, second and third line ART regimens in adolescents.

1 st line regimens	2 nd line regimens	3 rd line regimens
AZT+3TC + EFV/NVP	TDF+3TC + ATV/r or LPV/r	DRV/r a + DTG + AZT+3TC
TDF+3TC+EFV/NVP	AZT+3TC + ATV/r or LPV/r	DRV/r + DTG + TDF+3TC
ABC+3TC+EFV/NVP	AZT+3TC + ATV/r or LPV/r	DRV/r+ABC+3TC+EFV or NVP

AZT= Zidovudine, 3TC= Lamivudine, EFV= Efavirenz, NVP= Nevirapine, TDF= Tenofovir
 ABC= Abacavir, ATV/r= Atazanavir/ritonavir, Lopinavir/Ritonavir, DRV/r= Darunavir,
 DTG= Dolutegravir

According to the WHO recommendations, CD4+ threshold levels for starting ART evolved significantly over the last two decades. In 2006, all patients with CD4 counts less than 200 cells/mm³ and those in advanced clinical stages were eligible for ART. Then, the threshold increased to 350 cells/mm³ or less in 2010, then to 500 cells/mm³ or less in 2013. Since 2015, everyone infected with the virus has started ART immediately, regardless of their CD4 count or clinical stage (WHO, 2006, 2010, 2013, 2015).

In Ethiopia, the ART began as a fee-based program in 2003, and free ART was launched in 2005. Recognizing the need for ART, the government of Ethiopia developed the first antiretroviral (ARV) guidelines in 2003 to encourage the early implementation of ART. The guideline was revised in 2005, 2008, 2014, and 2018 in accordance with WHO guideline changes (FMOH, 2018).

Following a WHO recommendation for treatment start and its protocol, the Ethiopian national ART program has included DTG-based combination treatment as the preferred first- and second-line treatment for all people undergoing treatment (FMOH, 2018). The eligibility criteria for starting HIV medication were also revised on a regular basis in accordance with WHO recommendations (Table 2).

Table 2. ART initiation guidelines.

Year of guidelines	WHO clinical stage	CD4 criteria
Until 2012	Stage 4	≤ 200 cells/mm ³
2012–2013	Stages 3 or 4	≤ 350 cells/mm ³
Since 2014	All	≤ 500 cells/mm ³

Despite these incredible advances in HIV treatment, ART has limitations, most notably, successful HIV treatment requires daily doses of antiretroviral drugs for the remainder of the patient's life. However, forgetfulness, fatigue, hopelessness, stigma and discrimination, and beliefs are patient-level factors that influence ART success. These factors reduce the immunological benefits of ARVs, exposing clients to opportunistic infections and increasing the risk of treatment resistance and HIV transmission (Wasti et al., 2012).

Care and support

Care and support are comprehensive sets of services, including medical, psychosocial, physical, socioeconomic, nutritional, and legal support. These services are needed from the point of diagnosis throughout the course of HIV-related illness, regardless of the ability to access ART (UNAIDS, 2016). In addition to medical care, the well-being and survival of HIV patients relies heavily on psychological, economic, nutritional, and legal support. Continuous care and support services are imperative, starting from diagnosis and throughout the progression of HIV-related illness, irrespective of one's access to ART (UNAIDS, 2016). Dietary assessment, nutritional counseling, and food safety education are key components of medical management for maintaining weight and muscle mass.

Psychosocial support

Supporting individuals psychologically is a crucial aspect of treatment across all treatment stages. Examples of this support include counseling, spiritual support, measures to reduce risks, reminder devices for medication adherence, and establishing peer support groups (Adejumo, Malee, Ryscavage, Hunter, & Taiwo, 2015; Vreeman, McCoy, & Lee, 2017). Providing HIV treatment and support requires the involvement of a wide variety of people, including family members, nurses, doctors, community workers, and psychologists (WHO, 2016). Home-based care refers to the caregiving

responsibilities that individuals living with HIV/AIDS might undertake independently or that their family members or friends might undertake on their behalf, allowing them to remain in their residences.

Management of HIV-related diseases

HIV weakens the immune system, making individuals more susceptible to various infections and diseases. Some common HIV-related diseases and conditions include tuberculosis, pneumonia, diarrhea, and Candida infection of the mouth and throat (UNAIDS, 1998). Adequate nutritional advice should be provided to people living with HIV. In addition to treating physical symptoms including pain, cough, skin rashes, fever, and diarrhea, palliative care also deals with psychological problems like hopelessness and suicidal thoughts. There are affordable and effective drugs available to prevent many of the most common HIV-related diseases. Isoniazid is effective in preventing reactivation of latent TB, and cotrimoxazole is effective in protecting against many of the common pathogens (such as pneumococcus and salmonella) responsible for pneumonia and diarrhea and their complications (WHO, 1999, 2000).

Adherence to ART

Adherence is defined as a patient's ability to follow a treatment plan, take medications at the prescribed times and frequencies, and adhere to food and other prescription restrictions (Sahay, Reddy, & Dhayarkar, 2011). Successful long-term treatment of HIV requires near-perfect adherence to ART to prevent the emergence of drug-resistant HIV, which can lead to treatment failure (Kangethe, Polson, Lord, Evangelatos, & Oglesby, 2019). Adherence to HIV treatment is a challenge, especially for adolescents, because the course of illness in these individuals occurs during the perinatal period, and some adolescents do not know their HIV status (Hornschuh, Dietrich, Tshabalala, & Laher, 2017). HIV/AIDS in adolescents is mostly transmitted from the mothers (Namuli, Nalugya, Bangirana, & Nakimuli-Mpungu, 2021).

Non-adherence to ART continues to be the leading cause of treatment failure (Heestermans, T., J. L. Browne, S. C. Aitken, S. C. Vervoort, & K. Klipstein-Grobusch, 2016), and increases the risk of drug resistance and spreading of the virus to others (Sewamala et al., 2020). A study conducted in the United States found that the prevalence of non-adherence increased with age. Among 381 perinatally acquired HIV-positive children and adolescents during pre-adolescence and late adolescence/young adulthood, non-adherence increased from 31% to 50%, while the prevalence of

unsuppressed viral loads increased from 16% to 40% (Kacanek et al., 2019). Similarly, in a South African cohort of 933 adolescents aged 10 to 19 years who were followed for 3 to 4 years, adherence was assessed at baseline and two additional times. Adherence to ART is lower among adolescents living with HIV (ALHIV) than among adults and children (Zhou, Cluver, Shenderovich, & Toska, 2021). A study conducted in Addis Abeba, Ethiopia, among HIV-infected adolescents at three hospitals revealed that the magnitude of ART adherence was 79.1%, which was lower than the recommended threshold level (Firdu, Enquselassie, & Jerene, 2017).

Poor ART adherence is empirically proven to be associated with negative outcomes such as medication failure, viral mutations, and the development of drug resistance (Murphy et al., 2010), which further complicate the already limited second- and third-line treatment options available for patients (Johnston et al., 2012). Adolescents on HIV treatment have lower rates of viral load suppression and adherence than adults and children (van Wyk & Davids, 2019). Poor ART adherence is also associated with virological failure (Boyd et al., 2015). According to World Health Organization (WHO) guidelines, virological failure is usually defined as two consecutive viral load (VL) determinations above 1000 copies/mL after at least six months of ART and with adherence support between the two measurements (Labhardt et al., 2016). The threshold of 1000 copies/mL is used, since the risk of resistance development and disease progression is low below this level (Ford et al., 2015; Mocroft, Reiss, & Kirk, 2010).

The consequences of a virologically-failing first-line regimen include immunological and clinical stage progression (Nicastrì et al., 2005). Immunological failure was currently defined as a CD4 count that was consistently less than 100 cells/mm³ or less than 250 cells/mm³ following clinical failure. This allows for increased viral replication, which leads to an increase in the infection of new CD4+ T cells and, eventually, immune cell depletion (Tessa Heestermans, Joyce L Browne, Susan C Aitken, Sigrid C Vervoort, & Kerstin Klipstein-Grobusch, 2016).

A study conducted in northern Ethiopia showed that immunological failure was 3.8 times more likely in TB-coinfected patients than in TB-free people (Assefa, Gelaw, Getnet, & Yitayew, 2014; Zeleke, 2016), in Nigeria (Musa, Musa, Muhammed, Ibrahim, & Musa, 2015).

Therefore, the basic goals of ART are to prevent virus transmission, restore or maintain immune function, and reduce viral reproduction. High levels of HIV treatment adherence have been linked to better viral suppression outcomes. However, long-term adherence to ART remains difficult for a variety of reasons, including physical and psychosocial changes (Okawa et al., 2018). According to studies from sub-Saharan

Africa, patients' adherence to life-saving treatment regimens is likely to be influenced by a complex set of economic and social factors that challenge families while increasing health problems (Bermudez et al., 2016). In addition, treatment side effects such as dizziness, fatigue, nausea, vomiting, stomach burning, and lack of awareness of the indications for ARV treatment, such as missed doses of ARVs included in a single dose, also lead to adherence problems (Galea et al., 2018).

A systematic review revealed that fear of disclosure, forgetfulness, a lack of understanding of treatment benefits, complicated regimens, falling asleep, and being away from their medications were identified as barriers to patients' adherence in both developed and developing countries (Mills et al., 2006). Among these, forgetting to take drugs has been widely described as a major barrier to treatment adherence in people on ART (Dzansi, Tornu, & Chipps, 2020; Freeman, Gwadz, Francis, & Hoffeld, 2021a; Okuku & Dan-Jumbo, 2021; Sanjobo, Frich, & Fretheim, 2008).

Adolescents with HIV

Adolescence is a unique stage of life characterized by distinct health and developmental needs and rights. It is also time to learn knowledge and skills, develop capacities to manage emotions and relationships, and acquire the characteristics and talents that will be required for enjoying adolescence (10–19) and undertaking adult roles (WHO, 2020). It is characterized by rapid physical, psychosocial, cognitive, and emotional development, and sexual and reproductive maturation. It is a stage of increasing independence, social skill development, and learned behavior influenced by peer groups, and familial, cultural, and religious conventions (Lehtimaki, Schwalbe, & Solis, 2019; WHO, 2019).

In many countries, adolescent girls face inequality due to cultural and social norms, and many face gender-based violence, a lack of power to say no to child marriage, and sexual assault, which can be problematic when HIV is not disclosed. Despite continuing to engage in sexual activity, many adolescents choose not to disclose their sexual orientation (Grainger, 2017).

Adolescent HIV status disclosure is an important part of the care and treatment process and includes ongoing discussions about the disease as the child or adolescent grows intellectually, socially, emotionally, and sexually. Caregivers of vertically-infected children who are diagnosed at an early age are usually aware of the child's HIV status and may choose to delay or postpone disclosure for fear of stigma and being identified as a source of HIV transmission, and thus feel guilty, blamed, or rejected (Madiba &

Mokgatle, 2017). This may be because disclosure of HIV status increases risks of peer isolation, and the risk may outweigh any apparent benefits or overall gains (Hogwood, Campbell, & Butler, 2013).

Many of the adolescents' characteristics are related to one another and to adult population concerns. This shows that the high HIV incidence among adolescent females cannot be explained only by their biology and culture, but must be considered in the context of the general epidemic (Dellar, Dlamini, & Karim, 2015; Fleischman & Peck, 2015; Idele et al., 2014).

Furthermore, the age of sexual partners is a key factor that contributes to increased prevalence of HIV among adolescent girls and young women compared with that among similar-aged males. Most females are in age-diverse relationships with men who are one to ten years older than men (Maughan-Brown, Kenyon, & Lurie, 2014). As a result, different strategies are needed for adolescent girls aged 10–14 and 15–19 years.

mHealth

mHealth is a mobile communication technology in medical care that have been suggested as a method to improve the delivery of health services (van der Kop et al., 2018). There are different mHealth interventions, and they include short messaging service (SMS) reminders, gaming applications (apps), and interactive mobile apps (Cele & Archary, 2019). The WHO recommends peer-based interventions, community-based services, support groups, mobile technology, social media, or call centers to support healthcare services (WHO, 2016). Thus, based on this recommendation, different studies have been conducted in many areas using mobile technology to improve HIV treatment adherence among people living with HIV. Some of the mHealth tools used in research include alarms and phone calls, while diaries and calendars can be used to send brief reminders about the timing of ARV drugs, drug dosage, and appointments.

Text messages for HIV treatment support

Mobile phone text messaging is a unique mHealth variant because it allows researchers to personalize message content, promote bidirectional communication, and pair message timing to ART dosage schedules (Finitsis, Pellowski, & Johnson, 2014). Text messaging can generally be used to overcome geographic barriers, improve communication, and easily reaches marginalized rural areas where health services are

often difficult to access, or people who do not have time to access health services to get their health information.

A systematic review study evaluating the effectiveness of interventions designed to improve adherence in sub-Saharan Africa showed that some interventions, such as treatment supporters and cell phone short message services, were effective in increasing adherence in some settings but not in others, emphasizing the need for additional research (Bärnighausen et al., 2011). Similarly, a review of mobile phone text messaging interventions to enhance ART adherence in HIV-infected infants and children identified evidence from two trials supporting weekly text messages. It recommended conducting large RCTs for this intervention among adolescents and caregivers of children and infants with HIV (Horvath, Azman, Kennedy, & Rutherford, 2012).

Theoretical framework

Health Belief Model

The health belief model (HBM) is a social psychology model developed to explain and predict individual health behaviors. Rosenstock developed it in the 1950s with the intention of predicting which people would or would not take specific measures to avoid disease (Kozier, 2008). The model assumes that an individual took a health-related action if that person perceives susceptibility, severity of the condition, and benefits in taking action to reduce risk, and believes in his or her ability to successfully execute the action required to produce the desired outcome without barriers.

This adherence model defines adherence as a favorable health behavior shaped by an individual's perceptions, beliefs, and cues to action. Neglecting or not addressing these perspectives may lead to non-adherence. This study offers crucial insights into the psychological factors influencing drug adherence. This model effectively supports the development of mobile health interventions, utilizing constructs such as perceived susceptibility, severity, benefits, barriers, cues to action, and self-efficacy, which are known for predicting various health behaviors (Shariful, 2018).

Perceived susceptibility refers to how one perceives one's vulnerability to HIV, while perceived severity reflects the seriousness of AIDS. Overall, perceptions of the risk of HIV or AIDS are shaped by these views of susceptibility and severity. Perceived benefit reflects beliefs about the effectiveness of protective actions, while perceived barriers involve perceptions of drawbacks in such behaviors. Cues to action cover both internal and external influences that encourage a specific behavior, such as obtaining an HIV-antibody. Finally, self-efficacy refers to an individual's confidence in his or her ability to undergo a HIV-antibody test (Rosenstock, Strecher, & Becker, 1994).

Aim

Overall aim

The overall aim of this study was to develop, test the feasibility, and evaluate the effectiveness of mobile phone text messaging interventions in improving adherence to, and retention in, care among adolescents living with HIV in the south Ethiopia.

Specific aims:

- to investigate the effectiveness of mobile phone text message reminders in improving ART adherence among adolescents,
- to explore the experiences and needs of adolescents living with HIV regarding their ART adherence and retention in care in southern Ethiopia,
- to assess the intervention fidelity and factors affecting the process of implementing a mobile phone text messaging intervention among adolescents living with HIV and
- to evaluate the effectiveness of mobile phone text message reminders in improving ART adherence among adolescents living with HIV in Ethiopia.

Methods

Design

This thesis contains four studies described in four papers based on the UK Medical Research Council's (MRC) methodological framework for the development, testing, and evaluation of complex interventions (Craig et al., 2008). The first two studies are included in the development phase, the third and the fourth studies in the evaluation phase. In Paper I, available evidence on the effectiveness of mobile phone messaging in improving adherence and retention in care was reviewed. In Paper II, a qualitative study with an inductive descriptive approach was conducted to identify adolescents' needs and wishes. In Paper III, the study processes involved prospectively monitoring and testing the intervention was tested for fidelity and feasibility. Paper IV was designed as an individual randomized controlled trial (RCT) that compared standard care with intervention care and followed the CONSORT recommendations for RCTs (Schultz et al., 2010). Table 3 provides an overview of the four studies.

Table 3. Overview of the papers in this thesis.

Study	Design	Sample	Data collection	Analysis
I	Systematic review and meta-analysis	987 adolescents	Articles searched from PubMed, Embase, web of science, Cochrane library, and CABI	Meta-analysis
II	Inductive descriptive	18 adolescents	Qualitative interviews	Inductive content analysis
III	Convergent mixed method	10 adolescents 4 family members 2 healthcare providers 153 adolescents	Qualitative interviews Process indicators and records	Content analysis Descriptive statistics
IV	Individual randomized control trial	306 adolescents	Self-report, pill count, and viral load	Intention to treat analysis

The methodological framework

This thesis followed the methodological framework of the UK's MRC (see Figure 3) for the development, testing, and evaluation of complex interventions (Craig et al., 2008). The framework is flexible and allows different stakeholders to be involved in identifying key issues concerning study problems and interventions, as well as in designing and conducting research applying a variety of perspectives and approaches. In this thesis, a framework was used to develop an intervention that systematically promoted health behaviors and adherence to ART among adolescents using research evidence and appropriate theory to inspire adolescents to improve adherence to ART. When the research started, the latest available complex intervention framework was the 2008 version. The framework was revised in September 2021 to describe and also consider the core elements (context, developing and refining program theory, engaging stakeholders, identifying key uncertainties, refining the intervention, and economic considerations) that are important in all phases (Skivington et al., 2021).

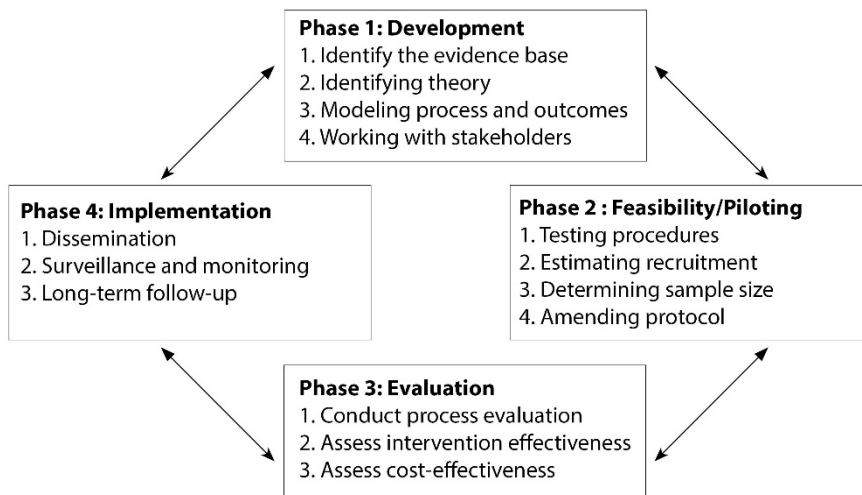


Figure 3. The MRC framework (Craig et al., 2008).

In the developmental phase, the effectiveness of mobile text messages in improving adherence was established through a systematic review (Paper I), while barriers to good ART adherence were explored in Paper II, shaping the message design using these findings. To address all the core elements, participants from various study sites were involved. A HBM was integrated as a theory to address both individual and contextual

barriers. Stakeholders including adolescents were engaged to offer insights and suggestions on the intervention identified during the project's development phase. The feasibility phase was important for understanding the context in which the intervention occurred, as well as for identifying facilitators and barriers to future implementation of the intervention in real-life contexts (Craig et al., 2008; Skivington et al., 2021). Prior to the full-scale study, key uncertainties in determining sample size, recruitment, intervention configuration, and timing of intervention delivery were identified and refined.

The process evaluation phase was dynamic and involved both quantitative and qualitative research methods (O'Cathain et al., 2019). This phase allowed for the evaluation of the intervention's effectiveness as well as for participant perspectives on the intervention, how it was evaluated, and the context in which it occurred (Oakley, Strange, Bonell, Allen, & Stephenson, 2006). An additional researcher who was not involved in the main evaluation of the trial effectiveness contributed to the process evaluation to ensure an independent observation. In the qualitative methods section of Paper III, interviews, helped to capture emerging changes in intervention, experiences of the intervention recipients, and unanticipated outcomes to explain the quantitative findings. The effectiveness of the intervention phase (Paper IV) was evaluated to compare the outcomes between the intervention and control arms. Therefore, the flow of the thesis was described using the three phases of the MRC framework (see Figure 4).

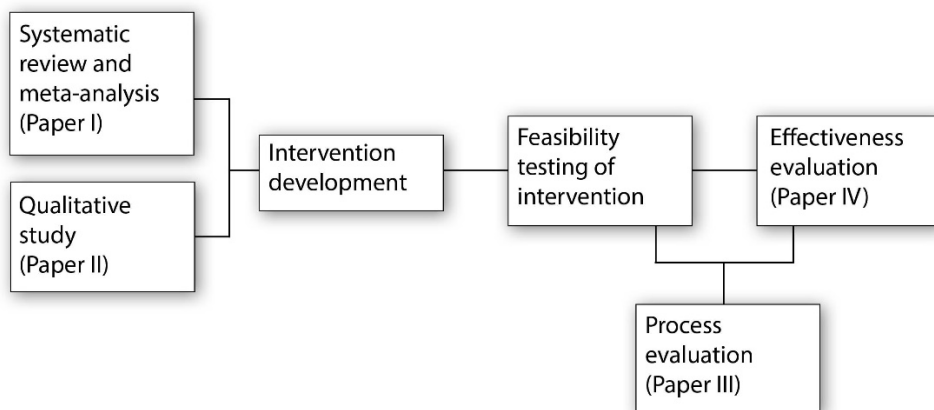


Figure 4. The flow of study from intervention development to evaluation of result.

Study setting

The study was conducted in health facilities that provide ART services at the Gamo, Gofa, Wolayita, Konso, and South Omo zones in the southern regions of Ethiopia. These zones are home to approximately 25 distinct ethnic groups and attract many foreign and domestic tourists. The hospitals and health centers included in this area were based on the existence of ART services and provide services for adolescents. Accordingly, Arba Minch General Hospital, Sawla General Hospital, Jinka General Hospital, Wolayita Specialized Hospital, Chenchha Primary Hospital, Dillfana Primary Hospital, Sawula Health Center, Konso Health Center, Sodo Health Center, Areka Health Center, and Boditi Health Center. The total number of people living with HIV in the selected facilities was 8,259. Of these, more than 465 were adolescents living with HIV (see Figure 5).

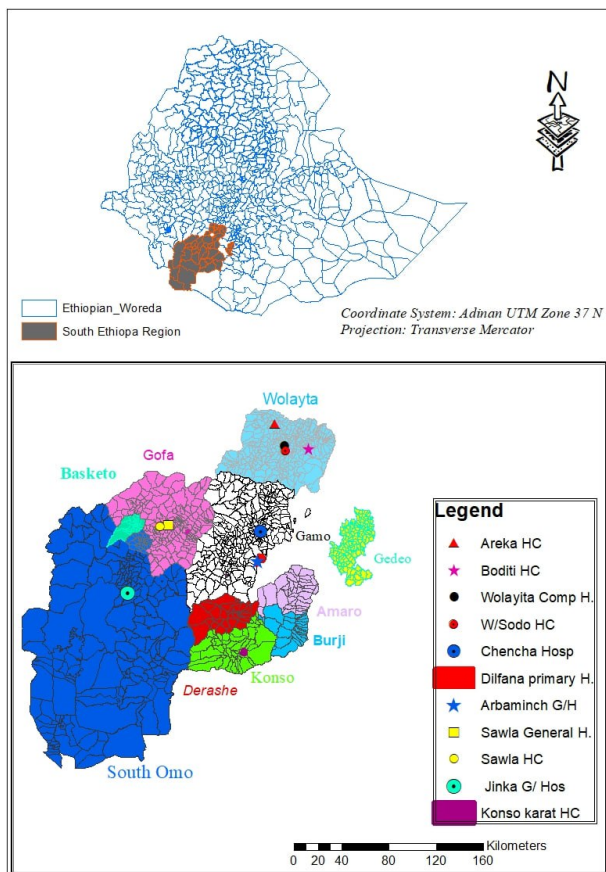


Figure 5. Map of study sites developed by using the coordinates of GPS.

Study participants

Paper I comprised studies relevant to the review topic, focusing on adolescents within a particular age range. It incorporated randomized controlled trials and non-randomized studies that employed mobile phone text messaging reminders as an intervention. In total, Paper I involved 987 participants, with individual study sample sizes varying from 14 to 332 individuals. Interventions such as phone calls, smartphone apps, and internet-based methods were not included in the studies.

Paper II involved 18 adolescents affected by HIV, covering a spectrum from early to late adolescence, comprising both genders from rural and urban areas. Moreover, Paper III included ten adolescents who participated in the intervention, four family members/relatives and two healthcare professionals from various ART clinics. For Paper IV, inclusion criteria involved 306 adolescents living with HIV receiving treatment at specific ART clinics, who provided consent, had the ability to read text messages, and resided in the study area for at least six months.

Intervention

A mobile phone text message reminder served as the intervention method in this thesis. Each participant received a mobile phone device and was instructed on how to use it for texting and deleting messages. They were provided with a unique four-digit code from Ethiopia Telecom, informing them of its importance to maintaining confidentiality, reducing any stigma associated with the message source, and easily distinguishing intervention text messages from other texts. Moreover, the mobile phone numbers of all participants were included in the messaging server, and their medication times were categorized according to their prescribed schedules. Tailored daily texts were then sent through automated software, 15 minutes before each person's medication time. Individual participant codes from the server were also used to track and cross-check sent or failed messages.

Standard of Care

All adolescents involved in the study received standard care services following Ethiopia's comprehensive HIV treatment and care guidelines for pediatric HIV/AIDS (FMOH, 2017). The standard care provided encompassed counseling, mental health support, nutritional assessment, and social and emotional support given by family, friends, and healthcare providers to adolescents diagnosed with HIV.

Counseling is vital at treatment initiation and throughout. Education on remembering ARV prescription details and fostering honest reporting of adherence, along with addressing mental health, performing dietary assessments, treating HIV-related and microbial infections, and providing support, were key in standard care. (see Figure 6).

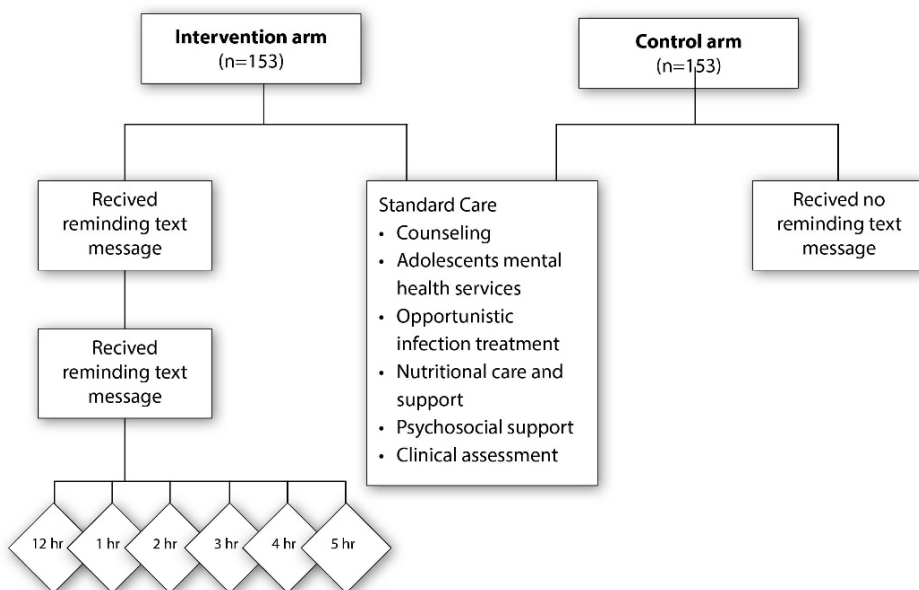


Figure 6. The procedure for assignment of study participants and messaging time category in intervention arm.

Data collection

Systematic Review

In Paper I, the search for primary articles was performed using a combination of keywords and truncated terms via a Boolean search strategy, and the authors connected synonymous terms with OR and different terms with AND (Table 4). Moreover, hand searching in the reference list of the screened articles, grey literature, and conference abstracts were reviewed. After removing the duplicates from the search hits, the first titles and abstracts were screened based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the full texts were read and assessed based on the exclusion criteria by authors of this thesis and other co-authors.

Table 4. Article search strategy to evaluate the effectiveness of mobile text messaging to improve adherence to ART until 18 August 2020.

No	Search terms and complete search strategy	Data bases	Number of articles found in the title	Restriction
1	(Mobile phone* OR cell phone* OR text reminder* OR text messages* OR phone based*) AND (HIV OR AIDS OR ART OR Antiretroviral therap*)	MEDLINE (PUBMED)	2160	No language and document restriction
2	(Mobile phone* OR cell phone* OR text reminder* OR text messages* OR phone based*) AND (HIV OR AIDS OR ART OR Antiretroviral therap*)	EMBASE	72	
3	HIV mobile phone reminders	WEB OF SCIENCE	202	
4	mobile phone reminders HIV	COCHRANE LIBRARY	102	
5	mobile phone reminders HIV	CABI	65	

Qualitative data collection

Based on the findings of Paper I, the author of this thesis developed a semi-structured interview guide (Appendix I) for Paper II, using constructs from HBM theoretical frameworks (Shariful, 2018), and discussed it with the research advisory committee and supervisors. Purposive sampling was applied to include adolescents from different contexts, as well as those who participated in and did not participate in other treatment-supporting interventions, such as a psycho-social peer support program. The interviews were conducted by the thesis author in a quiet and confidential setting at the respective health facilities, using audio-recording with consent.

In Paper III, adolescents assigned to the intervention arm were interviewed using a semi-structured interview guide (Appendix II) about their experience receiving text messages and the benefits of it, while family or guardians of those who did not receive the message, as well as healthcare providers, were interviewed about any changes in adherence and retention in care.

Quantitative data collection

In Paper III, occurrences such as adolescents transferring out, mobile device-related incidents, and any other adverse events were documented using an observational check list in each health facility, and the success and failure of messages sent from server records indicative of intervention fidelity were quantified.

In Paper IV, adherence, viral load, and retention in care data were collected at baseline, three, and six months. Self-reported adherence and retention in care data were collected on the same day using the REDCap app. However, blood sample collection and subsequent procedures were done by lab technician at each facility and sent to regional laboratory for viral load test. Then, viral load results data were collected post-blood sample analysis, using the patient's unique ART identification number from the participant cards and the trial participant code in the REDCap app.

Before collecting clinical data from participant cards and self-reported interviews, the thesis author provided one-day of training for the data collectors on how to use the mobile application, as well as on issues concerning confidentiality and security measures for the information being collected.

Data analysis

Qualitative data analysis

Inductive qualitative content analysis (IQCA) is a type of qualitative analysis in which text-based data, such as written transcripts of verbal or written documents, are used to understand the meaning(s) of the data set's content (Vears & Gillam, 2022). Paper II was based on an inductive analysis of the data, meaning that critical themes emerge out of the data (Patton, 1990).

The analysis began with a verbatim transcription of the data, which was then sent to all authors for independent familiarization with the data. The author of this thesis then reviewed the transcribed text multiple times to gain insight into the content and overall picture of the data. After that, the author of this thesis identified meaning units by reading each paragraph of the data based on each verbatim transcription of an interview answer. These meaning units were then combined into a condensed meaning unit and coding frame for analysis using NVivo software. The analysis was then discussed by all authors. Then, similar codes were identified and organized into one sub-theme, which was then evaluated, confirmed for accuracy with the transcripts, and discussed with all

three authors until agreement was reached. Finally, all sub-themes were re-categorized to overall themes as barriers and facilitators of HIV treatment adherence.

Quantitative data analysis

In Paper I, the Cochrane handbook for systematic reviews of interventions (Higgins, J. P., 2008) and the risk assessment tool for randomized and non-randomized trial designs (Sterne et al., 2016) were used to extract the data and assess quality. After evaluating the bias present in the studies included, each article was summarized with details about their general characteristics, the elements of the intervention, and the resulting conclusions or outcomes of the intervention.

Most of the articles assessed reported adherence to ART as a continuous outcome (mean adherence). As a result, the analysis relied on data such as the mean adherence rates and standard deviation. Where the standard deviation was not available, other effect measures, such as confidence intervals were converted to fit the model. Despite the small number of articles included in the review, the author of this thesis was interested in doing a meta-analysis in which pooled mean differences in adherence in one-way and two-way reminding message interventions versus standard of care were computed.

The study used a random effects model in Review Manager (version 5.4) to evaluate the overall mean difference between intervention arms, considering expected differences. For trials with the same interventions, a fixed effects model was used for subgroup analysis. In Paper IV, various statistical measures such as means, standard deviations, medians, interquartile ranges, frequencies, and percentages were employed to assess variable distributions and guide subsequent stages of analysis.

Following that, a bivariate analysis examined the relationship between factors and the primary outcome. Variables with p-values up to 25% were chosen for inclusion in the ordinal logistic regression model using a cumulative logit link function. Given the ordinal nature of ART adherence, generalized estimating equation (GEE) linear regression models were utilized to assess outcomes proportionately over time. GEE was also used to measure the intervention effect on VL data at two time periods in a single model using an exchangeable working correlation matrix that accounted for potential correlation due to within-participant dependencies over time.

Finally, the interaction effect of baseline and follow-up data, and model fitness were checked by comparing Naive and Robust standard errors. The model with the smallest values of information criteria was selected as the final model using STATA and R

statistical software for analysis. Finally, a p-value of less than or equal to 0.05 was used to declare statistical level of significance.

Mixed-method data analysis

In Paper III, a convergent mixed methods approach was employed to analyze quantitative and qualitative data concurrently, merging the findings to comprehensively address research questions within a corresponding timeframe (Demir & Pismek, 2018). Descriptive quantitative analysis was used to describe the number and percentage of messages sent, received, or failed, as well as the factors contributing to the failure of sent messages within the intervention group.

The IQCA was used to gain a holistic understanding of the perspectives shared by adolescents, parents, and healthcare providers. This method aimed to encompass insights into multiple facets such as how adolescents experienced receiving text messages, the technical elements of the intervention, family-related factors influencing adolescents' adherence, and the communication dynamics between healthcare providers and adolescents.

In this analysis, the raw data were divided into meaning units, condensed meaning units, codes, subthemes, and themes. The author of this thesis transcribed all the data, and all co-authors read the transcribed interviews and discussed codes. The author of this thesis and the second author in Paper III developed the sub-themes and themes and discussed them with all authors until consensus was reached.

The success or failure of the message, as well as its effectiveness, was evaluated using the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) approach, which was used as a process evaluation indicator and helped in the integration of quantitative and qualitative data.

Pre-understanding

Pre-understanding represents the initial perceptions and knowledge researchers have regarding a specific subject and its social context. This approach implies the proactive and systematic integration of this initial understanding by academics, presenting it publicly as a valuable addition alongside formal data and established theories in their studies (Gummesson, 2000). However, prior knowledge can influence the validity of the study. Bracketing is a method of proving the validity of the data collection and analysis process in qualitative research to minimize the possible negative effect of predictions that may contaminate the research process (Ahern, 1999).

The author of this thesis has a background in public health, has worked in academia, and has no clinical set-up experience. He has years of experience in both qualitative and quantitative research on infectious and non-infectious problems at the clinical and community levels. This prior experience of the topic was regularly reflected on and discussed during the research process.

Ethical consideration

This thesis was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki and its later amendments and approved by the Swedish Regional Ethical Review Board (Dnr 2019-03433), the National Research Ethics Review Committee in Ethiopia (MoSHE/RD/142/2869/20), and the Institutional Research Ethics Review Board at Arba Minch University (IRB-113/11). Permission to conduct the studies was obtained from the head or medical director at all health centers and hospitals.

Ethics concerns were raised at each level of the research procedure. The principle of a favorable risk-benefit ratio requires that risks to individual study participants be identified, justified, and minimized (Emanuel, Wendler, & Grady, 2008). Research with people living with HIV/AIDS requires special care in delineating and minimizing research-related risks such as attack on privacy or violations of confidentiality. Protecting the rights and welfare of those who volunteer to participate in research is a critical component of ethical research. The four pillars of medical ethics are autonomy, nonmaleficence, beneficence, and justice (DeVita, Hellman, & Rosenberg, 1985).

Autonomy is defined as the capacity to think, decide, and act freely and independently based on such thought and decisions (Gillon, 1985). In medical practice, autonomy is usually expressed as the right of competent adults to make informed decisions about their own medical care. The principle underlies the requirement to seek the consent or informed agreement of the patient before any investigation or treatment takes place. The principle of respect for people affirms the primary importance of allowing individuals to exercise their moral right of self-determination. However, this principle also implies that people who are not capable of self-determination should be protected, if necessary, by requiring permission from an individual authorized to consent on their behalf. Parents or legal guardians serve this important function for children who are younger than the age of maturity (Kauffman & Banner, 1995).

Permission refers to the agreement of a child's parent(s) or guardian with the participation of their child or ward in a clinical investigation (Roth-Cline & Nelson, 2013). Parental permission is held to the same standards as informed consent and is required (absent a waiver) for research involving children. The disclosure of

information required for voluntary and informed parental permission is the same as that required for informed consent and includes a discussion of the potential risks, benefits, and alternatives to research participation. In papers II–IV, both informed consent from age above 18 years and parental consent and adolescents’ assent for adolescents aged 10–17 years in the local language according to the national and international guiding principles for research involving minors were required. In addition, all participants were provided with written and verbal information about the study, as well as offered the right to withdraw at any point without additional explanation in their native language. All participants were guaranteed confidentiality.

The provision of a high-value mobile phone device may expose participants to physical theft if the technology is considerably beyond what is common among their peers. To minimize this risk, the mobile phone was as cheap as possible. Furthermore, the content of text messages is essentially unmanageable because texts may be seen by someone other than the intended recipient of the information. Text messages that include the type of treatment specified may result in the unintended disclosure of the presence of a medical condition, even if no details of the type of therapy are described.

The thesis did not contain any disease or virus-related information or details about specific medications in the text messages. Instead, it focused on delivering general motivational messages. In Paper III, we discussed the collective use of mobile phones among family members and their potential influence. During participant recruitment, the author of the thesis pre-assigned unique codes to the participants, which were also utilized in the data collection app. Throughout the intervention process, except for the intervention arm, blinding was maintained, and messages were transmitted through coded systems provided by an independent telecommunication company. This approach aimed to prevent any potential stigma associated with the messaging source.

Codes, field observations, and tape recordings were securely stored in locked cabinets at Arba Minch University. Electronically collected data was managed and stored in LUSEC at Lund University, a high-security platform compliant with general data protection regulation (GDPR) and the Swedish Data Protection Law, ensuring safe handling, storage, and analysis of the data.

Results

The findings of this thesis provide promising evidence that automated text message reminders improve treatment adherence among patients living with HIV in resource-constrained settings. In Paper I, only seven of the 2517 study titles assessed met the full text review criteria. Of those, two cohort studies were excluded due to significant bias concerns. Among the five randomized controlled trials analyzed, text messaging significantly improved treatment adherence in three studies, whereas in the remaining two, no significant differences were observed between the intervention and control groups. A meta-analysis revealed considerable heterogeneity among the studies ($I^2 = 78\%$). Then, a subgroup analysis was conducted aimed at deciding between implementing a one-way or two-way text message intervention for the subsequent Paper IV.

In Paper I, among 2517 titles assessed, only seven fulfilled the criteria for a thorough review of the full text. Two cohort studies were eliminated due to substantial bias. Out of the five randomized controlled trials examined, three articles demonstrated a significant improvement in treatment adherence through text messaging, while the remaining two exhibited no significant differences between the intervention and control groups. A meta-analysis revealed substantial heterogeneity among the studies ($I^2 = 78\%$). As a result, a subgroup analysis was performed to determine whether to implement a one-way or two-way text message intervention in the subsequent Paper IV.

In the subgroup analysis, fixed effects analyses were used to compare the effect of intervention in a similar group (one-way text message or two-way text message only), while random effects analyses allowed for inferences to a wider range of studies (Hedges & Vevea, 1998). However, the pooled evidence of the one-way text message, 0.05, and two-way text message, for improving ART adherence, was inconclusive. We decided on a one-way text message intervention rather than a two-way text message intervention because sending a message to confirm reception required adolescents to recharge their cell phone's mobile card.

Paper II identified barriers to adherence that could be addressed by the intervention specified in Paper I. In Paper II, 15 of 18 adolescents were vertically infected with HIV

from their mother at birth, and as the adolescents grew older, disclosing their status proved problematic for both healthcare staff and families. When HIV sero-status was reported to adolescents for the first time, whether by a healthcare provider or a family member, it was identified as having a detrimental influence on the adolescent's mental well-being, and they became emotionally distressed. The main barrier to adherence that needed to be addressed by adolescents was forgetting medication or medication time, a lack of privacy, perceived stigma, and a lack of support.

For anyone to get support from healthcare professionals, family, friends, religious organizations, and other organizations, one must disclose his or her HIV status. However, in Paper II, adolescents felt ashamed to disclose their HIV status, and as a result, many of them received inadequate support (financial, material, moral, and emotional care) and paid unnecessary money for transportation by attending care-facilities that were further away to avoid stigma. When their HIV status was not disclosed, the adolescents experienced self-stigma and fear when collecting treatment pills from hospitals, forgot to take medication on time, or purposefully failed to take the prescription.

In Paper III, the process evaluation findings revealed that 99.4% of the 30700 reminder messages sent were successfully delivered. However, the causes of 0.6% of unsuccessful messages were identified qualitatively, such as an electric power system, an uncharged phone battery, and caregiver influence on phone usage, all of which contributed to the intervention's failure. Interruptions to the local telecommunications networks and local electric power were key structural barriers. Moreover, technical issues in server management and individual factors such as lack of phone ownership among early adolescents at household-level were described as additional barriers.

In Paper IV, the mobile phone text message increased adherence by 34% in six months. At baseline, there was no significant difference in ART adherence between the intervention and control groups. Over a six-month period, high adherence increased while low and moderate adherence decreased proportionally in the intervention arm compared to the control arm (see Figure 7).



Figure 7. Comparing the level of adherence in an intervention- and control arm in a 6-month period.

Similarly, the odds of having a high VL decreased by 30%, whereas the odds of having an undetectable VL increased as visit time changed from baseline to six months (see Figure 8).

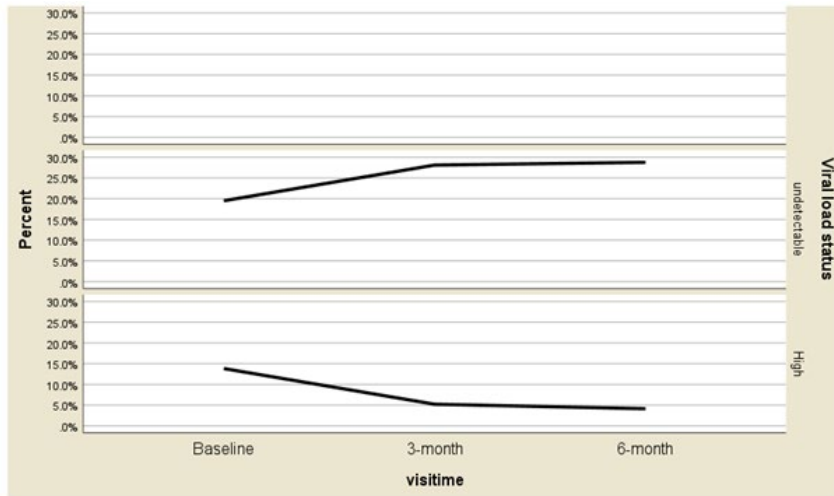


Figure 8. Comparing viral load status for six months among adolescents living with HIV.

Discussion

General discussion of the findings

We found that automated text reminders led to a 34% improvement in adherence to ART at 6 months of treatment. It was feasible to deliver this service through locally configured automated text message delivery systems designed by locally trained staff. Intervention fidelity was high, with >99% of the messages delivered to the intended audience. The availability of mobile phones was a prerequisite for delivering the study interventions, which needs to be taken into consideration when planning such interventions. Findings from each phase of the MRC model service served as critical inputs to the subsequent phase. Key results from each phase are discussed in the following paragraphs. In the developmental phase of text message intervention, the available evidence from different databases was searched and systematically reviewed (Paper I). Thus, the pooled evidence of the effectiveness of text reminders in improving adherence to ART remains inconclusive due to small studies that enrolled non-adherent treatment initiators, and the fact that few interventional studies have been conducted among the adolescents age group. The reviewed papers had considerable heterogeneity. Variations in clinical, methodological, or statistical features could be the source of the heterogeneity. Clinical heterogeneity is described as differences in participant characteristics (e.g., age, baseline conditions, ethnicity, comorbidities), types or timing of outcome assessments, and intervention parameters (e.g., dose, frequency of dose, interventionist training) (Jpt, 2008). Methodological heterogeneity refers to differences in study design and the potential of bias. Statistical heterogeneity is indicated by a variation in the intervention effects reviewed across studies and is caused by either clinical or methodological heterogeneity, or both (J. Higgins & Green, 2011).

In the meta-analysis, statistical heterogeneity was evaluated using tools such as the I-squared statistic (I^2). Higher statistical heterogeneity signals significant differences among individual research findings, while lower heterogeneity suggests greater similarity. In Paper I of this thesis, we observed elevated statistical heterogeneity due to the limited number of studies in those areas.

In the meta-analysis, statistical heterogeneity was assessed using measures such as the I-squared statistic (I²). Higher statistical heterogeneity shows considerable variation in individual research findings, whereas lower heterogeneity indicates higher similarity. Therefore, in Paper I of this thesis, we found high statistical heterogeneity due to the small number of studies in these areas.

Similarly, a more recent review on the use of text message intervention for improving adherence to ART in patients with HIV was inconclusive (Sun et al., 2023). A study by Ugandan showed that reminder text message intervention fails to improve adherence in adolescents and young adults (Sebastian Linnemayr et al., 2017). In Kenya, however, patients who received reminder text messages had significantly higher rates of ART adherence and viral suppression when compared to controls (Lester et al., 2010).

Adolescents living with HIV/AIDS might experience stigma, discrimination, or emotional distress related to their condition. This psychological burden can affect their motivation to adhere to treatment, impacting their mental well-being and adhering to their treatment schedule due to forgetfulness or a lack of routine in their daily lives. Thus, in Paper II of the thesis, the experiences of adolescents in treatment and care were explored, and medication adherence challenges such as forgetting to take medication on time, privacy concerns, and stigma were identified. Similarly, another study revealed forgetfulness as the primary reason for missed ART doses among PLWH. Factors like stable housing and support reduce forgetfulness, whereas depression, poverty, stigma, and substance misuse elevate its likelihood (Freeman, Gwadz, Francis, & Hoffeld, 2021b). Another study identified several barriers to ART adherence, including forgetfulness, a lack of familial and social support, a poor diet, a low socioeconomic status, feelings of hopelessness and depression, doubt in treatment efficacy, rejection, and stigma (Farhoudi et al., 2018).

Text message reminders aid in maintaining medication routines, reducing missed doses, improving adherence, and result in better health outcomes. The design of Paper IV was based on a systematic review (Paper I) and a qualitative study (Paper II) that utilized mobile phone text reminders to address both intentional and unintentional medication non-adherence. Thus, in this thesis, the automated daily text message reminders sent to adolescents' mobile phones improved adherence by 34% when compared to the control arm. In Paper IV of the thesis, the average effect of proportion of adherence increased, while VL decreased across the 6-month intervention period. A study conducted in Kenya, on the other hand, revealed that daily reminder text messages had no effect (Pop-Eleches et al., 2011). The sending of reminder text messages was not scheduled in accordance with an individual's actual medication time; this could be the reason for no improvement in adherence in the Kenya study. Similarly,

text reminder messages sent to HIV-positive adolescent and young adult patients in two Ugandan clinics showed little effect on ART adherence. Furthermore, there was no difference in adherence between one-way and two-way messages (S. Linnemayr et al., 2017).

Apart from evaluating the effectiveness of the mobile phone text message intervention, we identified factors associated with poor treatment outcomes. These factors included the number of pills returned during refills, instances of missed medication, and lack of adolescent participation in hospital-based psychosocial peer support, indicating poor adherence. On the other hand, adolescents who were unaware of their daily pill dosages, changed their ARV regimens, or who missed scheduled appointments showed significant association with high viral loads.

All these factors are important for adolescents' treatment adherence because they are linked to medication perceptions, patient-physician relationships, and communication or counseling in the clinic setting. Missed appointments cause problems in all healthcare systems and have a substantial impact on how hospitals manage cases, because patients who fail to follow up must be tracked down and reintegrated into the system.

Evaluating the process of intervention implementation was essential for gauging how closely the intervention adhered to its intended procedures and protocols, ensuring fidelity and proper execution. However, factors related to individuals, families, and the broader structural context can influence the implementation process of an interventional study. In Paper III of the thesis, a few participants reported lost/damaged/stolen phones, local telecommunication networks, local electric power disruptions, and multiple users on a single cell phone were barriers to proper intervention. Similarly, a study conducted in Metro Manila, Philippines, showed that the local context for cellular phone infrastructure and operational challenges, such as multiple users on a single cell phone, has an impact on text messaging interventions (O'Connor et al., 2022). However, intervention fidelity in the Philippines was low (77.9%), compared to 99.4% in Paper III. The difference could be due to customizing reminder text messages based on adolescent's own preferences and using four-digit coded communications for confidentiality and security. This approach also helps in differentiating the message source without having to read it.

Structural barriers such as local networks and electric power disruptions were identified as barriers to intervention implementation (Paper III). A systematic review study on mHealth in Africa showed that unreliable internet, network, and electrical power are significant barriers to text message intervention delivery (Aranda-Jan, Mohutsiwa-Dibe, & Loukanova, 2014). For mHealth to be successful, the implementation area

must have infrastructure such as a consistent internet connection, electricity, and a network (Haberer, Kiwanuka, Nansera, Wilson, & Bangsberg, 2010; Siedner, Haberer, Bwana, Ware, & Bangsberg, 2012). Furthermore, technical, or expert knowledge for configuring and maintaining of the intervention platform, may be unavailable locally, and even if available, a lack of experience in configuring it might hinder implementation, because technical training is normally necessary.

Therefore, the level of collaboration and engagement of government authorities is crucial for the success of mHealth implementation (Lester et al., 2010). Furthermore, healthcare providers need to build the necessary skills and organizational capabilities to manage digital health data (Leon, Schneider, & Daviaud, 2012). Reminding text message interventions may fail due to high illiteracy rates and user preferences (Hoffman et al., 2010). However, modifying message types and cooperating with mobile technology companies to address illiteracy may increase scalability (Mahmud, Rodriguez, & Nesbit, 2010).

Methodological considerations

Conceptual and theoretical frameworks

The methodological considerations of the thesis were based on the MRC framework involving various factors crucial for designing, implementing, and evaluating mobile phone text messages. In the developmental phase of this framework, the HBM theoretical basis and evidence for designing interventions should be understood, considering the context, target population, and potential mechanisms of change (Kozier, 2008). In Paper I, the evidence for the effectiveness of text message intervention was reviewed in many studies. Due to the small number of studies done in adolescent populations, the evidence obtained from these studies was inconclusive. Based on the findings of Paper I, and Paper II was planned and designed to explore adolescents' experiences with treatment and care. It aimed to gather their input regarding text message reminders for incorporation into the intervention, about all aspects of the HBM theoretical framework.

The HBM provides insights into the cognitive and perceptual influences on health behaviors. It highlights an individual's beliefs about HIV/AIDS, treatment benefits, barriers to treatment, and self-efficacy. Improving ART adherence involves emphasizing treatment benefits, providing barrier support, boosting self-efficacy, and using reminders. Following intervention development, feasibility testing was performed

at Arba Minch General Hospital to assess practicality and acceptability before full implementation, employing both quantitative and qualitative methods.

After starting the full study, process evaluation was conducted for Paper III to evaluate the intervention's implementation process, including barriers and the mechanisms of change, to understand how and why the intervention works. Thus, we followed the RE-AIM framework to assess whether the intervention was delivered as intended and monitored fidelity to assess adherence to protocols and procedures. The RE-AIM framework enables a comprehensive assessment of interventions, going beyond efficacy evaluation. It helps us understand delivery practicalities, and reached populations, adoption rates, and long-term sustainability, enhancing research translation into practice for improved public health impact.

In the outcome evaluation phase, adherence, retention in care, and VL were measured to compare the effect of the intervention in relation to the two arms (Paper IV). However, there is no gold standard for estimating ART adherence (Williams, Amico, Bova, & Womack, 2013). Self-reporting is the most commonly used method of measuring adherence in standard clinic settings (Morisky, Green, & Levine, 1986). It is susceptible to recall, and the issue of underestimating and overestimating reported adherence has been raised due to social desirability biases (Berg & Arnsten, 2006). In Paper IV, to avoid overestimation or underestimating, composite adherence measurements such as self-reporting, pill count, and VL were used.

Validity

The ability of a study to exactly measure what it intended to measure is referred to as its research validity. When conducting experimental research, it is critical to consider both internal and external validity since these aspects influence both the experimental design and the generalizability of the findings.

Internal Validity

Internal validity addresses whether the study design, conduct, and analysis answer the research questions. A study is internally valid if the study conclusions represent the truth for the individuals studied, since the results were not likely due to chance, bias, or confounding because the study design, execution, and analysis were correct. Bias is defined as any deviation of outcomes from the truth (Buring, 1987). Randomized controlled trials are considered the gold standard in research for evaluating the effectiveness of interventions. However, just because a study is randomized does not mean it is unbiased (Lewis & Warlow, 2004). Some of the biases in RCTs are discussed below.

Selection bias

Selection bias occurs when the characteristics of the study groups differ. This difference can occur for a variety of reasons, including allocation concealment. The Cochrane criteria defines selection bias as the systematic differences between baseline characteristics of the groups that are compared (J. P. Higgins & Green, 2008). In Paper IV, there was a good balance of baseline characteristics between the intervention and control groups, showing that the randomization and allocation were successful by taking place at a single institution and were not prone to selection bias. To avoid unnecessary exclusion of adolescents without a mobile phone and to minimize selection bias due to their economic position purchasing a mobile phone, all adolescents were given a mobile phone.

Information bias

Information bias occurs during the data collection procedure from the various study groups, including handling, recording, and reporting of information (Buring, 1987). It can be categorized into different parts.

Social desirability bias

Social desirability bias is the tendency to under-report socially undesirable attitudes and behaviors and to over-report more desirable attributes (Latkin, Edwards, Davey-Rothwell, & Tobin, 2017). The setting in which self-reporting adherence data was collected by health professionals working in the same facilities via an interview may have a significant influence on the study's validity. However, in the thesis (paper II–IV), health professionals at specific ART clinics facilitated data collection and played no other roles. Furthermore, the data collectors who were independent of ART clinics, and those that participated in the baseline and outcome data collection, were different, conducting the interviews in a private and separate room.

Reporting Bias

The way research results are presented can be influenced by their nature and outcome, leading to what is known as reporting bias. For instance, studies demonstrating ineffective interventions might not get published, resulting in access to only a portion of the relevant evidence on a subject. This bias comes in various forms, such as publication bias and outcome reporting bias. Selective reporting of outcomes can occur when only certain outcomes that show positive or significant results are reported, while others are omitted (Dwan et al., 2008; Sterne, Egger, & Moher, 2008).

Publication bias occurs when studies with positive or statistically significant results are more likely to be published than those with negative or inconclusive results (Thomas

& Heneghan, 2021). In a systematic review, if unpublished or grey literature (studies not published in peer-reviewed journals) with negative findings are not included, it can skew the overall conclusions and favor the effectiveness of an intervention when it might not be as effective. To reduce the impact of publication bias, we conducted a comprehensive screening and review of published, unpublished, and conference articles written in any language (Paper I). To minimize outcome reporting bias (Paper IV), the study protocol was pre-registered in the pan-African clinical trials registry, a composite adherence measurement was used, and CONSORT recommendations were followed (Schultz et al., 2010).

Informational spillover

In the context of an interventional study, informational spillover refers to the unintended dissemination or sharing of information between different groups or individuals participating in the study. This sharing of information could potentially influence outcomes or behaviors, affecting the integrity or effectiveness of the intervention being studied. Spillovers were more common in cluster-randomization than in individual-randomization (Hayes, Alexander, Bennett, & Cousens, 2000).

However, in an individual RCT where participants are randomly assigned to treatment and control groups, information spillover could occur if individuals in the control group gain access to information about the treatment. This could lead them to adopt elements of the treatment, thereby hiding the difference between the groups and affecting the study's outcomes. In the thesis (Paper IV), the intervention was implemented at an individual level using a confidential four-digit code to prevent spillover effects. Nevertheless, in the process of recruiting participants, computer-generated random numbers were used, resulting in a situation where a small number of adolescents from the same families were assigned to different intervention arms, potentially leading to spillover effects on outcomes.

Confounding

A confounder is a factor associated with both an observed cause and the outcomes under investigation (Bovbjerg, 2019). It may hide a true association or wrongly display an apparent association between treatment and outcome when no such relationship exists (Weiss, 2006). In this thesis, we tried to decrease unmeasured or residual confounding variables by ensuring balanced baseline characteristics and using multivariable analysis to account for those variables known to influence the outcomes presented in Paper IV. Despite these efforts, there is a possibility of unmeasured or residual confounding effects associated with treatment adherence and specific factors within the models.

Chance

Statistical significance is not always indicative of causation. If selection, information, or confounding bias cannot explain the outcome, chance may serve as an alternative explanation. The emphasis on bias over chance lies in biases' ability to produce significant but erroneous outcomes. One of the first practical procedures and statistical principles to consider when planning a clinical trial to address a research question is sample size (Kirby, Gebiski, & Keech, 2002). A study using a small sample size might fail to capture exact differences between groups, posing ethical concerns. As power increases, so should the sample size. Once the study's effect has been determined, the 95% confidence interval (CI) should be utilized to describe the level of uncertainty surrounding the effect estimate rather than power (Goodman & Berlin, 1994). The greater the effect, the less likely it is to be overlooked (Penelope, Brasher, & Brant, 2007). The power used in this thesis was 90, and the sample size was large, making the effect differences between study arms due to chance more unlikely.

External validity

External validity refers to the extent to which the findings of a study can be generalized or applied to settings, populations, or conditions beyond the specific context in which the research was conducted. It is a measure of how well the results obtained from a study can be validly and reliably applied to other people, places, or times (Egger, Smith, & Altman, 2008; Rothwell, 2005). External validity, as defined in Rothman's modern epidemiology, encompasses both scientific and statistical generalization. Scientific generalization, inherent in epidemiological studies, enables the creation of a cohesive, potentially causative biological hypothesis applicable across various clinical or epidemiological contexts. In contrast, statistical generalization holds paramount importance in sampling as it ensures the final sample accurately mirrors the statistical makeup of the source or target population (Rothman, 2012). External validity can occur only if the study is first internally valid (Gay, 2006).

In this thesis, both scientific and statistical generalizations pose no issues. There is a likelihood of their applicability to analogous contexts owing to the participants sharing similar experiences despite differences in age, gender, and culture. Furthermore, the adolescents included in the study were drawn from geographically diverse areas with varied cultural backgrounds, thus increasing the probability of their representation in the recruited population. In papers II and III of the thesis, given the qualitative nature of the research, contextual elements might impact the extent to which the study findings can be generalized.

Trustworthiness

Trustworthiness is the most commonly used criterion for evaluating qualitative content analysis, and it is often expressed using terms such as credibility, conformability, and transferability (Lincoln & Guba, 1985). In papers II and III, qualitative content analysis was used to analyze qualitative data.

In Paper II, adolescents were carefully selected for inclusivity across genders, geographic areas, and urban-rural contexts. The analysis involved directly transcribing the data and identifying themes through an inductive approach. Paper III included adolescents, along with their families or guardians, and healthcare professionals in the intervention group. Like in Paper II, the analysis consisted of transcribing the data directly and generating themes through an inductive process.

Credibility

To ensure the credibility of content analysis, an appropriate data collection method needs to be used (Graneheim & Lundman, 2004). Credibility deals with the focus of the research and refers to the confidence in how well the data addresses the intended focus (Polit & Beck, 2004). The thesis focused on adolescents' HIV treatment and care experiences, as well as treatment barriers (Paper II), and adolescent, family, and professional interviews were conducted to explore their experiences and issues with mobile text messaging interventions (Paper III). There is no universally approved sample size for qualitative studies because the appropriate sample size is determined by the study's objective, research questions, and data richness.

Conformability

Conformability refers to the objectivity, that is, the potential for congruence, between two or more independent people about the data's accuracy, relevance, or meaning (Lincoln & Guba, 1985). Conformability of findings means that the data accurately represents the information that the participants provided, and that the interpretations of that data are not invented by the inquirer (Polit & Beck, 2004). This is especially important if the researcher decides to analyze the latent content (noticing silence, sighs, laughter, posture, etc.) in addition to manifest content. This means the findings must reflect the participants' voice and conditions of the inquiry, and not the researcher's biases, motivations, or perspectives. In this thesis, the audio data was transcribed to verbatim text and organized into sub-themes and themes using inductive content analysis, and exemplary quotations were provided in papers II and III.

Transferability

Transferability refers to the extent to which the findings can be transferred to other settings or groups (Polit & Beck, 2004). In qualitative research, transferability is synonymous with generalizability, or external validity, in quantitative research. Transferability is established by showing readers how the research study's findings could be applied to various contexts, situations, times, and populations. The context in which public health programs operate can have a substantial impact on their success and implementation.

An intervention that has been shown to be effective in one context may be ineffective in another, even if it can be done there (Wang, Moss, & Hiller, 2006). In Paper III of this thesis, the five-dimension components of the RE-AIM framework were used to collect information about the intervention setting, implementation, personnel and circumstances, and findings (Glasgow et al., 2019). Reach, effectiveness, and maintenance—three of the five RE-AIM dimensions—all work at the individual level, that is, for the people who are expected to benefit. Adoption, implementation, and maintenance are focused on the staff and setting levels, which are typically different, and address internal and external context challenges that have a significant impact on the population's health.

Conclusion and implications

The findings of this thesis provide promising evidence that automated mobile phone text message reminders improve adherence among patients living with HIV in resource-constrained settings. We found that adolescents living with HIV who received reminder text messages on their phones during medication had higher adherence rates and better viral suppression. Adherence to ART increased proportionally, which is associated with a high undetectable VL in the blood.

Effective adherence to ART has significant benefits for individuals living with HIV, and public health initiatives addressing HIV/AIDS control. It helps in suppressing the HIV virus, decreasing the VL to undetectable levels, benefiting individual health, and reducing the risk of viral transmission. Adhering to the prescribed medication regimen also lowers the likelihood of drug-resistant HIV strains. Moreover, maintaining adherence enables individuals to lead active lives, maintain employment, follow education, and actively participate in society, promoting their overall well-being. On the other hand, non-adherence or missed doses might result in the virus mutating and developing resistance to medications, potentially compromising treatment efficacy.

The advantage of server-based text messaging is that it sends reminders to many study participants over a wide geographical area, requiring minimal human resources following the initial setting up process. It could be a key part of a comprehensive strategy supporting ART adherence. The intervention, developed with input from adolescents themselves, enabled tailored care for individuals living with HIV, and integrated their preferences into the messages. As a result, the group receiving the intervention had better adherence and viral suppression than the control group. The adolescents' involvement and shared decision-making in the intervention process had added benefits, which may have implications for policy, practice, and future research.

Policy and practice implications

In Ethiopia, HIV treatment and care are provided at all levels of the health system, including primary, secondary, and tertiary care. At the primary level, ART is accessible in health centers and primary hospitals. Digitalizing healthcare improves patient-

centered care, quality, and efficiency. The success of mHealth requires strategic, integrated national initiatives as well as the government's responsibility in arranging infrastructure setups. This requires strategic and integrative policy decisions at the national level to be realized as concrete action plans.

The National HIV/AIDS Strategic Plan (NSP) from 2021 to 2025 (FMOH, 2020) developed various strategies for intervention and partnered with various government sectors to mainstream and reduce the HIV burden. However, Ethio telecom, the main telecommunication provider in the country, was not considered as to be a partner in the NSP (FMOH, 2020). This may affect the implementation and integration of mHealth within the routine care system.

Recent telecommunications improvements in the country offer a valuable opportunity to expand mobile phone-supported HIV treatment for adolescents. With reduced airtime fees and wider network coverage, using text messages on mobile phones for healthcare has become more feasible and easier to integrate into the routine healthcare system.

Future research

We identified several topics for future research:

- **Feasibility and impact of scaling up the intervention to all ART sites.** For the success of mobile phone text message reminder implementation, and to integrate it within the routine healthcare system, organizational collaboration and engagement of government authorities is crucial. Future research could focus on facility readiness to configure a mobile phone text message intervention platform in all ART-providing clinics.
- **Reminders for illiterate and disabled people.** Further implementation study is needed to address the real-world impact of symbol and visual-based message reminders among people who are unable to read the prescription, medication time, and appointment date using mobile phone reminder text.
- **Facilitating adolescent transition to adult care.** Adolescents who did not participate in the hospital-based psychosocial peer support had poor adherence to ART and were stigmatized. These adolescents, however, were transitioned to an adult clinic because of their age being above 19 years. Future research could focus on adolescent readiness for the transition from pediatric to adult care clinics, as well as on organizational readiness for assessing adolescent transition.
- **Virological impact of the interventions.** Despite strict adherence to the medication schedule, some patients in the intervention group had high viral loads. As a result, additional research on virological outcomes is needed.
- **Long-term impact and economic evaluation of the interventions.** More research is needed to evaluate the long-term impact of text message reminders sent via mobile phones on improving treatment adherence. In addition, further research on cost-utility, examining mobile health intervention costs and their impact on quality of life, is crucial. This evidence will help policymakers, healthcare professionals, and decision-makers compare and prioritize interventions, optimizing resource allocation and enhancing healthcare spending for improved public health.

አጭር የጥናቱ ማጠቃለያ/Summary/

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የሰዎችን በሽታ የመከላከል አቅም የሚያዳክም ቫይረስ (ኤች.አይ.ቪ) ኢትዮጵያን ጨምሮ ከሰሃራ በታች በሚገኙ የአፍሪካ ሃገራት ታዳጊ ወጣቶች ላይ ከፍተኛ የጤና ችግር ሆኖ ቀጥሏል። ይህም የተጠናከረ የመከላከል ጥረት እንደሚያስፈልግ ያመለክታል። በሕክምና የተሻለ የጤና ሁኔታ እንዲኖር ኤች.አይ.ቪ በደማችው የሚገኝባቸው ሰዎች የፀረ-ኤች.አይ.ቪ መድሃኒትን በአግባቡ መውሰድ አስፈላጊ ነው። ይሁን እንጂ ኤች.አይ.ቪ በደማችው የሚገኝባቸው ሰዎች በቂ ድጋፍ ከሌላቸው በየቀኑ የፀረ-ኤች.አይ.ቪ መድሃኒታቸውን በአግባቡ መውሰድ ቀላል አይሆንላቸውም።

የፀረ-ኤች.አይ.ቪ መድሃኒትን በአግባቡና በተገቢው በመውሰድ ቫይረሱን በከፍተኛ ሁኔታ መግታት እና የበሽታውን እድገት መግታት ይቻላል። በሌላ በኩል የፀረ-ኤች.አይ.ቪ መድሃኒት በአግባቡና አለመውሰድ በጉርምስና ዕድሜ ክልል ለሚገኙ ወጣቶች ዓለም አቀፋዊ ችግር ነው። ይህም ለህክምናው ውድቀት እና መድሃኒት ለተለመደ ቫይረስ መከሰት ከፍተኛ እገዛ ያደርጋል። ከኤች. አይ. ቪ ጋር አብረው የሚኖሩ በጉርምስና ዕድሜ ክልል የሚገኙ ወጣቶች የጸረ-ኤች.አይ.ቪ መድሃኒቶችን በአግባቡ አንዳይወስዱ የሚያደርጉ ማህበራዊ እና ኢኮኖሚያዊ ችግሮች ሊያጋጥሟቸው ይችላል። ሳይወስዱ ወይም ዘግይተው የሚወስዱት መድሃኒት መጠኖች፣ ሕክምናውን ማቋረጥ እና መቆራረጥ፣ እንደዚሁም ከተገቢው መጠን በታች አልያም በከፊል መውሰድ ደካማ የመድሃኒት አጠቃቀም መኖሩን ጠቋሚዎች ናቸው።

በኤች. አይ. ቪ የተያዙ በጉርምስና ዕድሜ ክልል ለሚገኙ ወጣቶች የኤች.አይ.ቪ ዉጤታቸውን ለሌሎች ለማሳወቅ አይፈልጉም። ከዚህም የተነሳ ማገኘት የሚገባቸውን ድጋፎችን (የገንዘብ፣ የቁሳቁስ፣ የሞራልና፣ የሥነ ልቦና) እያገኙ አይደሉም። ከዚህም በተጨማሪ በአቅራቢያው የሚገኙ የህክምና ተቋማትን መጠቀም ሊያስከሰት ይችላል ብለው የሚያስቡትን መገለል በመፍራት ሩቅ ወዳሉ የህክምና ተቋማት በመሄድ ለአላስፈላጊ የመጓጓዣ ወጪ ይዳረጋሉ። በዚህም ምክንያት በአቅራቢያቸው ከሚገኙ የጤና ተቋማት መድሃኒቶችን ለመውሰድ መፍራት እና የትምህርት ቤት እና የሆስፒታል ቀጠሮ መደራረብ ህክምናውን በአግባቡ እንዳይከታተሉ እና በእንክብካቤ ውስጥ እንዳይቆዩ እንቅፋት እንደሆነባቸው ታዉቋል።

ህክምናን መከተልን ከሚጎዱ ዋና ዋና መሰናክሎች መካከል ምግብ መግዘት ባለመቻል ምክንያት በባዶ ሆድ የፀረ-ኤች.አይ.ቪ መድሃኒቶችን መውሰድ፣ በሽይረሱ መኖራቸውን ሚስጢራዊነትን መጠበቅ እና በኤች.አይ.ቪ ምክንያት ወላጅን በማጣት የሚመጣ በቂ ያልሆኑ የቤተሰብ ድጋፍ ናቸው። ከዚህም በላይ በብዙ ጥናቶች ላይ የተደረገ ሳይንሳዊ ትንተና እና በጉርምስና ዕድሜ ክልል ከሚገኙ ወጣቶች ጋር የተደረጉ ጥልቅ ቃለ-መጠይቆች ወጣቶች በታዘዙት መሰረት መድሃኒቶችን ለመውሰድ መርሳት በተገቢው መልኩ አለመውሰድ መሰረታዊ እንቅፋቶች መሆናቸውን ያመለክታሉ።

የፀረ-ኤች.አይ.ቪ መድሃኒት አወሳሰድን ለማሻሻል በአለም ጤና ድርጅት ከሚመከሩት ቁልፍ ስልቶች አንዱ የማስታወሻ አጭር የጽሁፍ መልእክት መጠቀም ነው። እነዚህ የሚያስታውሱ አጭር የጽሁፍ መልእክቶች ሕመምተኞች መድኃኒቶቻቸውን እንዲወስዱ ለማስታወስ ለመርዳት፣ በቀጠሮ መሰረት ያለቀውን መድሃኒት ሳይረሱ እንዲወስዱ፣ እና ሕክምናቸውን እንዲቀጥሉ ለማስታወስ ይረዳቸዋል። ይሁን እንጂ ውጤታማነቱ እና እነዚህ አጭር በመደበኛ እንክብካቤ ውስጥ እንዴት እንደሚዋሃድ የሚያሳይ እስካሁን ግልጽ ማስረጃ የለም። በታዳጊ ወጣቶች ላይ የተደረገ የተለያዩ ጥናቶች እንደሚያሳዩት፣ የመድኃኒት መውሰጃ ሰዓትን ለማስታወስ በሞባይል የሚላኩ አጭር መልእክቶች በአንዳንድ ጥናቶች ላይ ህክምናን በማሻሻል ረገድ ውጤታማ ሲሆኑ በሌሎች ደግሞ ምንም ለውጥ አላሳዩም። በመሆኑም በታዳጊ ወጣቶች ላይ የመድኃኒት መውሰጃ ስርዓትን ለማስተካከል ተብለው የተጠኑ ሳይንሳዊ ጥናቶችን ሰብስቦ ስንገመግም የመድኃኒት መውሰጃ ስርዓትን ከማስተካከል አንጻር ያለውን ውጤታማነት ይህ ነው ብሎ ለመናገር ያስችግራል። ይህም ዕድሜያቸው ከ10 እስከ 19 ባሉ ታዳጊ ወጣቶች ዙሪያ የተደረጉ ጥናቶች ጥቂት ከመሆናቸው የተነሳ ተጨማሪ ጥናት እንደሚያስፈልግ ይጠቁማል።

በመሆኑም በደቡብ ኢትዮጵያ በታዳጊ የዕድሜ ክልል ላይ የሚገኙ ወጣቶች እና ተንከባካቢዎቻቸውን በጉርምስና ዕድሜ ላይ የሚገኙ ወጣቶች የፀረ-ኤች.አይ.ቪ ሕክምናና መድሃኒትን በተገቢራቸው ጊዜ አክብረው እንዳይወስዱ የሚያደርጉ ምክንያቶች በጥናቱ ተለይተዋል። ስለሆነም በሞባይል ስልክ የሚላከው አጭር የጽሁፍ መልዕክቶች የፀረ-ኤች.አይ.ቪ መድሃኒት አወሳሰድን ለማሻሻል እንደሚጠቅሙ ተሳታፊዎች ላይ ያላቸውን ውጤታማነትና ፈላጎታቸው በጥናቱ ተረጋግጧል። በመሆኑም ለእያንዳንዱ ሰው የመድኃኒት መውሰጃ ሰዓትን የሚያስታውስ የኮምፒውቴር ቴክኖሎጂውን ከኢትዮ-ቴሌኮም ጋር በማሰተሳሰር በማንኛውም ሰዓት በራሱ ጊዜ የሚታዘዝ የአጭር የጽሁፍ መልእክት መላኪያ ስርዓት በመንደፍና ለስድስተ ወራት ከትትል በማድረግ ውጤታማነቱ ተገምግሟል። በጥናቱ ውስጥ ከተሳተፉ 306 በጉርምስና ዕድሜ ላይ ከሚገኙ ታዳጊዎች ውስጥ ግማሾቹ የመድሃኒት መውሰጃ ሰዓትን የሚያስታውስ አጭር የጽሁፍ መልእክት የሚደርሳቸው ሲሆን ግማሾቹ ግን አያገኙም። ከተላኩ ከሰላሳ ሺህ በላይ መልዕክቶች መካከል 99.4% ያህሉ ለተቀባዮች ደርሰዋል። ለተከታታይ ስድስት ወር አጭር የጽሁፍ መልእክት በተቀበሉት ላይ መድሃኒትን በተገቢው መልኩ መውሰድ የተሻለ ሆኖ ተግኝቷል። እንደዚሁም በደማቸው

ውስጥ የሚታየው የኤችአይቪ ቫይረስ ልኬት መጠንም አጭር የጽሁፍ መልእክት በሚደርሳቸው የጥናቱ ቡድን የተሸለ ቫይረሱን የመቆጣጠር ዉጤት ተመዝግቧል።

በመሆኑም በጉርምስና ዕድሜ ክልል የሚገኙ ታዳጊዎች መድሃኒቶቻቸውን በአግባቡ እንዲወስዱ ለመርዳት መደበኛ አጭር የጽሁፍ መልእክት ማስታወሻ እንዲተገበር ይመከራል ። ህንፃ እቅድ ተግባራዊ ለማድረግ ተጨማሪ ግብዓቶችን መጠቀም እና የመንግስት መሪዎች ጠንካራ ቁርጠኝነትን ይጠይቃል። በተጨማሪም ከኤች አይ ቪ ጋር የሚኖሩ ወጣቶች እና ተንከባካቢዎቻቸው ንቁ ተሳትፎ ማድረግ አለባቸው።

Acknowledgments

This research was conducted within the Department of Health Sciences at the Medical Faculty of Lund University, in Sweden. Many important people have contributed to this thesis. I would like to express my sincere gratitude to:

- All adolescents, parents, and healthcare providers who shared their knowledge and experiences with me.
- All ART providers and data clerks at the research sites played an important role in facilitating and contributing to data collection, resulting in the success of this study.
- Mr. Tesfahun Mengistu and Mrs. Zeritu Bekele (head of the ART clinic at Arba Minch General Hospital) for your invaluable support during the feasibility test phases of the project.
- Professor Inger K. Hallström, my main supervisor. I am very grateful for the opportunity to work with you on the 'Child and Family Health' research group. Your extensive expertise, research dedication, and focus on understanding the challenges faced by children and adolescents have been truly remarkable. I deeply appreciate your endless support, quick feedback on my drafts, and guidance in creating well-structured research papers.
- Associate professor Degu Jerene, my co-supervisor. I deeply appreciate your remarkable guidance throughout my PhD journey. Your insightful advice, constructive input, and willingness to engage in meaningful discussions have been instrumental in my development. Your patience and openness have truly enhanced my research journey. I feel incredibly fortunate to have had the opportunity to learn from your extensive expertise in clinical research. Your supervision has played a pivotal role in shaping my scientific career, and I credit many of my accomplishments to your sincere support and guidance. I am thankful for your support in enrolling me in the complex intervention course, which served as a gateway to my current pursuit of a PhD.

- Special thanks to Wuletawu Wonte for your invaluable contribution in coding the message pushing software and for managing servers. Your support was crucial for a smooth start to the intervention process.
- Kabtamu Tolosie Gergiso for generating random numbers for study participants and supporting the data analysis.
- I would like to express my gratitude to Dr. Tamiru Shibiru of Arba Minch University and Magnus Persson for their tremendous administrative support.
- I am grateful to Jon Ulvsgård for his support with the poster layout and distribution of my research findings.
- Anna Blomgren, for support with the layout of this thesis as well as fine illustrations.
- Habtamu Abebe for your professional contribution in mapping the study areas.
- I would like to express my appreciation to my current and former colleagues and friends within the Child and Family Health research group at Lund University for their valuable contributions, discussions, and support. Your insights and feedback provided during research seminars have been incredibly helpful. I am especially thankful to Angela Afua Quaye for her guidance and for graciously sharing her experience.
- Mrs. Banchi Million. I appreciate your kindness in introducing me to a new environment and showing me around the shopping centers. This made it easy for me to find all the materials I needed.
- To my friends and colleagues at Arba Minch University's College of Medicine and Health Sciences—Tekilu Teshome, Dr. Alemayehu Shanko, Abinet G/Michael, Alemayehu Bekele, and Dr. Zerihun Zardo—thank you for the enjoyable moments during coffee breaks and lunch. Belay Boda: Your continuous support, particularly during the data collection, has been invaluable. Mulugeta Shegaz: Your encouragement and expertise in my field have meant a lot to me. I deeply appreciate your support, kindness, and friendship.
- I extend my heartfelt thanks to my mother, Aleke Alto, and to Tunje Tanga for nurturing me with love and encouragement. Your prayers and unwavering support throughout my life have been instrumental in my achievements. You have been my walking stick and driving force.
- Ayelech, my love, I want to thank you for your unlimited and immeasurable support, and Neamin (Niku) and Mariena, my dearest in this world for making me happy and forget feeling tired.

- I owe deep gratitude to my beloved brothers (Asrat Tunje, Ayele Tunje, Anteneh Tunje, Gizachew Tofilo, and Solomon Tofilo), for their love, prayers, and constant encouragement during the entire process of my research.
- My heartfelt gratitude goes to my lovely sister, Birtukan Tunje, for her constant encouragement.
- I am very grateful to Aseggedech Amistu for her incredible support given to my family, which has been vital for my career success and achievement of my goals.
- This thesis was made possible due to the generous financial support provided by the Swedish Research Council for Health, Working Life and Welfare (FORTE).
- Above all, I thank and praise the almighty God for providing me with favor, unique opportunities, and countless blessings in my life.

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