Improving ART adherence among HIV positive adolescents and youth using an eHealth intervention: a field study in Mombasa, Kenya

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Promotor: Prof. Dr. Kristien Michielsen

Dissertation presented in the 2nd Master year in the programme of

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Date 8/8/2016

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Foreword

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Abstract

English

This thesis describes a mixed methods evaluation of an eHealth based intervention to improve ART (antiretroviral therapy) adherence among HIV infected adolescents and youth (HIVAY) in Mombasa, Kenya. A total of 92 participants were recruited from HIVAY receiving ART in the second largest government hospital in Kenya, the Coast Provincial Hospital. The intervention consisted of a digital online platform tailored to the needs and recommendations of HIVAY, aiming to improve ART adherence among participants by providing peer support, HIV related information and the possibility to interact with health care professionals.

Qualitative data was collected before the start of the intervention by conducting focus group discussions (FGD) with HIVAY and with health care professionals involved in the treatment of HIVAY. Quantitative data was collected from questionnaires filled out by the same participants at baseline and after three of months of intervention. The questionnaires assessed various psychosocial outcomes including HIV related knowledge, perceived importance of ART adherence, perceived self-efficacy of adherence and intentions for future adherence as well as behavioral outcomes.

The results of the FGD showed that fear for disclosure of one’s HIV status was considered the biggest barrier to maintaining ART adherence among HIVAY. Other frequently mentioned barriers were related to the lack of adolescent- and youth-friendly health care services and to the psychological burden of living with HIV. The FGD results also suggest that HIVAY’s knowledge of HIV and ART shows various gaps and inconsistencies. Quantitative data showed slight improvements in HIV/ART related knowledge, perceived importance of adherence, perceived self-efficacy in maintaining adherence and intentions to adhere in the next three months, however this effect was found not to be statistically significant.

The findings in this study suggest the potential benefits of an eHealth intervention based on a digital online platform, but further studies with longer interventions and stronger methodological designs are needed before recommendations can be made.
Nederlands

Deze thesis beschrijft de evaluatie van een eHealth interventie met als doel het verbeteren van de therapietrouw van adolescenten en jongeren die leven met HIV in Mombasa, Kenia. Een groep van 92 deelnemers werd gerekruteerd uit adolescenten en jongeren met HIV die in behandeling zijn in het tweede grootste publieke ziekenhuis van Kenia, het Coast Provincial General Hospital. De interventie bestond uit een digitaal online platvorm dat werd ontwikkeld in samenwerking met HIV-positieve adolescenten en jongeren. Het digitaal platform beoogde om de therapietrouw van de jongeren te verbeteren door het bieden van peer support, correcte informatie omtrent HIV en de mogelijkheid om met professionals uit de gezondheidszorg te communiceren.

Voor de lancering van het digitaal platform werd kwalitatieve informatie verzameld door het voeren van focus groep discussies met HIV-positieve adolescenten en jongeren, alsook met professionals in de gezondheidszorg die nauw betrokken zijn met de behandeling van deze jongeren. Kwantitatieve informatie werd verzameld aan de hand van vragenlijsten die de deelnemers invulden bij de lancering van het digitaal platform en na drie maanden interventie. De vragenlijsten beoordeelden de kennis van de deelnemers omtrent HIV en hun behandeling, het belang dat zij hechten aan goede therapietrouw, de mate waarin ze zichzelf in staat achten om de therapie nauwkeurig te volgen en hun intenties tot therapietrouw de komende drie maanden. Ook werd hun gedrag met betrekking tot therapietrouw, alsook een aantal socio-demografische eigenschappen beoordeeld.

De resultaten van de focus groep discussies gaven aan dat angst voor het bekend worden van hun HIV-status de hoofdreden was waarom HIV positieve adolescenten en jongeren hun medicatie niet innemen zoals werd voorgeschreven. Verder toonden de kwalitatieve data aan dat de kennis van de deelnemers omtrent HIV en hun behandeling enkele hiaten vertoonde. De resultaten van de kwantitatieve data suggereerde een beperkte verbetering van de gemeten variabelen, maar was over het algemeen niet significant.

Dit onderzoek suggereert dat een eHealth interventie die gebruik maakt van een online digitaal platform, de therapietrouw van adolescenten en jongeren met HIV kan verbeteren hoewel er verder onderzoek met een sterkere methodologie nodig is Alvorens aanbevelingen kunnen gemaakt worden.
**Introduction**

1. Current situation

1.1. Human Immunodeficiency virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS)

The disease we know today as Acquired Immune Deficiency Syndrome (AIDS) was first recognized in 1981 when increasing numbers of young homosexual men inexplicably fell ill and died to infections that their immune systems should have been able to fend off (1). Four years later, in 1985, scientists managed to isolate the cause of AIDS, a retrovirus called Human Immunodeficiency Virus (HIV) (2). It was a characteristic immunologic feature found in the blood of AIDS patients that lead to that discovery: a gradual depletion of a specific type of white blood cells called CD4+ T-lymphocytes or CD4+ T-cells (3). This gradual depletion of CD4+ T-cells is the hallmark of HIV infection, with AIDS being the final disease stage when the immune system is no longer capable of fending off opportunistic infections.

Over the last three decades, HIV infection has rapidly spread across all continents becoming a pandemic infection with a devastating impact on global health, and sparking research towards finding a cure. Scientists discovered that HIV emerged after zoonotic (cross-species) infections with simian immunodeficiency viruses from African primates (4). Two main types of HIV have been distinguished, HIV-1 and HIV-2, which can be categorized further into different subtypes, groups and strains. The discovery that HIV consists of a group of genetically diverse viruses has proven to be one of the biggest obstacles in finding treatments and vaccines. The genetic diversity of HIV is a result of error prone enzyme systems in the replication cycle of a viral particle and a short replication time. HIV is a retrovirus, which means that after entering a human host cell, it is capable of transcribing its viral RNA to DNA, which in turn has to be inserted in the DNA of the host cell in order to produce new viral particles. Viral enzymes that accommodate the conversion of the viral HIV RNA to DNA lack the ability to repair the frequent ‘errors’ made during this process, also known as mutations. After insertion in the host DNA, the host cell is instructed to produce viral proteins and enzymes, which are assembled to form new viral particles (5). Mutations will now be present in every new particle produced by that host cell. Luckily, only a very small proportion of the genetic mutations that occur during the replication cycle of HIV will result in particles with genetic advantages, such as increased resistance to the immune system and or to antiretroviral agents.
While HIV can infect many different types of human cells, replication can only take place in CD4+ T-lymphocytes, also known as T helper cells. CD4+ T-cells play an important coordinating role in the adaptive immune system, and gradual depletion of this cell type will ultimately lead to failure of the immune system.

Stopping the further spread of the virus can only be achieved by reducing the number of new infections. In order to do this, we must understand how HIV is transmitted from one person to another(1). In infected humans, HIV particles can be found in blood, seminal fluids, rectal and vaginal fluids and in breast milk. These fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the bloodstream of an uninfected (seronegative) person for transmission to occur. Mucous membranes are found inside the gastro-intestinal tract and inside the uro-genital tract, including mouth, rectum, penis and vagina. Once the mucosal barrier is breached, HIV particles can enter the bloodstream and spread throughout the body.

As in most infectious diseases, the risk of becoming infected with HIV after exposure to the virus depends on a number of factors. These include the route of transmission, the ‘virulence’ of the specific HIV subtype, and the susceptibility of the host to infection. For HIV, the route of transmission is the most determining factor whether an individual becomes infected or not, with parental exposure (eg. needlestick injury) giving the biggest risk of infection. Since HIV particles are present in seminal fluids, blood and breast milk, it can be transmitted both vertically, mother-to-child transmission (MTCT), and horizontally (sexual intercourse, blood transfusion, injected drug use).

Once a person becomes infected with HIV, three stages of infection can be identified, although symptoms and rate of progression infection can differ greatly from one person to another. Around one to four weeks after HIV infection occurs, flu-like symptoms, such as fever, rash, sore throat, headache and swollen glands in the neck region are frequently reported, indicating an acute viral infection. However, this first stage of acute viral infection during which the seroconversion takes place, can go by without causing any symptoms. During the second stage of HIV, the adaptive immune response changes its focus to the production of highly effective antibodies. Antibodies appear in the blood within two weeks after the initial infection and persist for life, but it may take up to three months before they are detectable by HIV-tests (5). These have strong neutralizing activity, but are unable to clear the infection completely due to the rapidly mutating HIV particles. The level of HIV replication in the body stabilizes and tends to remain relatively stable for about 10 years, even without initiating therapy. The amount CD4+ T-cells will gradually deplete over the course of the years, up to the point where the
immune system fails to fend off infections that are easily preventable in healthy individuals. Once these opportunistic infections start appearing, one has reached the third stage of HIV infection, commonly known as AIDS. It must be noted that HIV infection in people with immature immune systems, such as newborns, behaves differently compared to HIV infection in adults.

1.2. HIV pandemic

A pandemic is generally defined as an infectious disease that has spread through human populations across multiple continents, or in the case of HIV, worldwide. Going into the third decade of the HIV pandemic, it was estimated that more than 36 million people have died of AIDS-related illnesses, making it one of the deadliest infectious diseases in history. In 2014, it was estimated that there were 36.9 million people living with HIV (PLHIV) with over 25.8 million in Sub-Saharan Africa alone (6). While only 12% of the world population lives in Sub-Saharan Africa, this region accounts for over 69% of all people living with HIV, making it the epicenter of the HIV pandemic (7). Global efforts have managed to stop and even reverse the further spread of the HIV pandemic. A turning point was achieved when a new treatment for HIV was found to be effective. The use antiretroviral therapy (ART) in the treatment of HIV infection has managed to change the HIV/AIDS landscape completely by drastically increasing the survival rate of HIV infected people and reducing both vertical and horizontal transmission (8). This has changed HIV from a lethal disease into a manageable chronic disease, compatible with long survival. This explains why the number of PLHIV is still growing, while the number of new infections has been steadily declining. At its peak in 1997, about 3.7 million people were newly infected with HIV each year, while in 2012 an estimated 2.3 million new infections were registered. The number of AIDS related deaths has also been reduced since it peaked in 2004 from 2.5 million people to 1.6 million people in 2012.

While the global decline in new HIV infections shows that current prevention strategies and interventions are bearing fruit, Sub-Saharan Africa is still home to 70% of all new HIV infections and over 75% of AIDS related deaths. Within Sub-Saharan Africa, there are also significant regional differences. Eastern- and Southern African countries are most afflicted, with adult prevalence rates of 15% and higher. For example the Republic of South Africa has the biggest HIV epidemic in the world with 17% of all PLHIV and adult prevalence rates up to 19.1% (9).
Kenya has the fourth largest epidemic with over 1.6 million PLHIV and an adult prevalence rate of 16%.

The uneven distribution of HIV prevalence, new infections and AIDS related deaths between SSA (Sub-Saharan Africa) and the rest of the world is even more distinct in the adolescent population. In 2012, it was estimated that there were 2.1 million adolescents (10 - 19 year) living with HIV, 82% of whom lived in Sub-Saharan Africa. With over 42% of all new HIV infections occurring in this age group, it is safe to say that this population is at the epicenter of the pandemic (UNAIDS report 2013). In 2012, HIV was the second leading cause of death for people in this age group globally, while in 2000 it was not even in the top 10. Between 2005 and 2012, AIDS-related deaths among adolescents increased by about 50% (from 71,000 in 2005 to 110,000 in 2012), compared to a 32% decrease among all other age groups during the same period (10). These alarming epidemiologic trends emphasize the need for dedicated efforts towards preventing new infections and providing access to HIV care in this population.

1.3. Being born and growing up with HIV

In order to put an end to the HIV pandemic, it is essential to stop further transmission of HIV. Preventing new HIV infections in infants deserves priority for several reasons. Not only does HIV infection at a young age have lifelong repercussions, which results in a huge burden of disease for both the individual and countries with high prevalence, it can also be prevented effectively with relatively low-resource interventions (6).

It is estimated that over 90% of the HIV positive infants (aged 0 – 1 years) are infected through mother-to-child transmission (MTCT), which means the infection occurred during pregnancy, at birth itself or during the following year. Several routes of transmission have been reported. During pregnancy, transmission may occur when viral particles manage to surpass the natural barrier of the placenta. During the partus (birth process), the child is directly exposed to blood and other body fluids that contain viral particles and can cause transmission. A review estimated that the risk of transmission before or at the time of birth is around 20% if the mother is untreated (11).

A third route HIV infection in infants, is through breastfeeding, since viral particles can be found in breastmilk of HIV+ mothers. Shortly after the introduction of antiretroviral m(ARV) as a treatment for HIV in the early 90s, studies reported their ability to reduce risk of MTCT. ART reduces the viral load in the blood, which in turn reduces risk of transmission. Since then, increasingly effective ARV regimens and global efforts to improve access to maternal and
pediatric ART have reduced MTCT even further. An UNAIDS report estimated that expanding access prevented more than 670,000 children from acquiring HIV from 2009 to 2012 (6). The number of newly infected children has gone down 58%, from 520,000 in 2000 to 220,000 in 2014. Despite this substantial progress toward reducing new pediatric HIV infections, there were still approximately 3.4 million children living with HIV and 230,000 AIDS-related deaths among children in 2011 (12). Once again sub-Saharan Africa is affected disproportionately with over 90% of HIV-infected children living in this region, and HIV being one of the leading causes of death in this age group.

The progress achieved in the last decade was mainly by providing high coverage of ART to pregnant women living with HIV in regions with high HIV prevalence and low resources, such as Sub-Saharan Africa. This remarkable progress in reducing new infections through MTCT shows that dedicated efforts on a global level have the potential to make a significant impact on the HIV pandemic. In order to reduce MTCT even further, ART coverage should be expanded to include women who breastfeed their child and measures to reduce risk of transmission during birth. These measures, which have been implemented in Western countries and proven to be effective and However, many of the countries with high prevalence of HIV in pregnant women do not have the resources to achieve that. Mothers living with HIV in high income countries have access to formulated milks to feed their infants without risk of transmission, while in many developing countries children are dependent on breastmilk for survival. This puts HIV+ mothers who don’t have access to ART for a heart wrenching dilemma: risk of infecting their infant with HIV or risk malnutrition and other serious illnesses for which breastmilk offers protection, such as diarrhea and pneumonia.

Other interventions that have proven to reduce MTCT are an elective caesarian when giving birth, provide ART to newborns preemptively and at policy level primary prevention of new HIV infections among women of reproductive age and provide counseling and testing services for pregnant women (13).

Unfortunately, many PLHIV, including pregnant women, are unaware of their HIV status. An UNAIDS report shows that of the 36.9 million people living with HIV globally, 17.1 million do not know they are infected and need to be reached with HIV testing services. Improving testing services has to be accompanied by improving access to ART, since it is immoral to diagnose people with HIV without being able to provide a treatment. The UNAIDS report estimated that globally 22 million PLHIV do not have access to treatment, including 1.8 million
children. In low-resource settings, less than 25% of children living with HIV currently receive treatment (6).

Untreated HIV infection in infants is characterized by rapidly progressing disease and by death occurring at a young age (14). Data from the Sub-Saharan African region has shown that without ART more than half of HIV-infected infants die by age 2 years, compared to 8% of uninfected infants. Even with ART, mortality rates in HIV-infected children are estimated to be at least 30 times higher than mortality rates among uninfected children (15). The high mortality rates in HIV infected infants are mainly due to opportunistic infections and an increased susceptibility to common childhood illnesses such as diarrhea, pneumonia, malaria, and malnutrition (16).

Recent evidence has suggested that the progression of HIV is much slower in a substantial percentage of perinatally infected children, in contrary to what was generally believed (17, 18). Over the past decade, substantial numbers of perinatally infected HIV positive adolescents and youth (PHIVAY) have been presenting to health care services for the first time during adolescence. For example, a study in Zimbabwe showed that, of the 86 HIV-positive adolescent patients attending the two acute primary health care clinics, 81% were previously undiagnosed, even though they had clinical features that suggested long-standing HIV infection (19).

Available data suggest that about one-third of infected African infants are so called ‘slow progressors’ with a median life expectancy of more than 10 years, even without diagnosis or treatment (19). This has resulted in a huge burden of undiagnosed HIV disease among adolescents in Sub-Saharan African countries such as Zimbabwe, which may adversely affect progress made towards reducing new infections in this population. Another consequence of these ‘slow progressors’, is that HIV as cause of ill-health in older children is often overlooked, since it was assumed that they would have died by that age if infected perinatally.

A study on perinatal HIV transmission reported that children infected through breastfeeding are more likely to be ‘slow progressors’ than children infected during the pregnancy or during the partus (20). The timing of HIV infection could have a critical impact on the anti-HIV immune response because of the major changes to the immune system that happen in the post-partum period (20). This suggests that regions such as Sub-Saharan Africa, where children are fed almost exclusively through breastfeeding, have a bigger proportion of ‘slow progressors’.

In high-resource countries, pediatric prevention and treatment guidelines have been implemented over the last decade and have changed the outcome of HIV infection in infants from rapidly lethal to a chronic and manageable disease compatible with long survival (21).
The first generation of PHIVAY has given us the chance to broaden our knowledge on the impact of HIV and its treatment on human development and to develop interventions to address the specific needs of this population.

As with many chronic diseases, HIV infection acquired in the perinatal period affects the development of the person, both physically and psychologically. Children growing up with HIV without access to treatment have a reduced linear growth rate and a reduced Body Mass Index (BMI) compared to healthy children (15, 22). The onset of puberty, which is considered as the start of adolescence, is also delayed in children growing up with HIV. A study on the long-term outcomes in PHIVAY has suggested that diagnosis during the first weeks of life, regular health care and access to ART helped HIV infected children to maintain normal height, weight and BMI scores up to adolescence, even with the limited therapeutic options that were available in the first years of their lives(23). In Sub-Saharan Africa however, the beneficial effect of early initiation of ART on growth patterns might be compensated by other causes of poor growth, such as malnutrition (24).

The incidence of severe neurological diseases in HIV infected children, in particular HIV-related encephalopathy, have decreased dramatically since highly active ART was introduced (25). However, several studies have reported that PHIVAY may suffer from less severe neurocognitive diseases which can substantially affect their quality of life, relationships, school achievements and risk taking behavior (22). Various cognitive deficits, such as attention and memory problems, have been reported in studies evaluating the effects of HIV on the central nerve system, as well as a higher risk of mental health problems(26). The impact of mental health problems on quality of life and on functioning as an adult is profound and should not be underestimated (27).

While the beneficial effects of ART on the development of HIV infected children has been documented and probably outweigh the negative effects, the potential neurotoxic effect on the development of the brain is unclear and subject to further research, especially when considering that more children will reach adolescence thanks to increasing ART coverage.

Complications related to prolonged ART have been documented well in adults and seem to affect PHIVAY as well. Metabolic complications such as lipodystrophy, dyslipidemia, insulin resistance, lactic acidosis, and bone loss may develop at young age, and contribute to their already heavy burden (28). In adolescents the impact of these changes in body fat distribution
should not be underestimated, as they affect the body image which in turn could discourage them from taking their medication as prescribed(22, 29).

Other complications related to prolonged ARV treatment include cardiovascular problems, renal failure, liver failure and hematological problems(28). The exact impact of ARV and long standing HIV infection is not completely understood, and further research is needed in order to adequately address the unique challenges of this first generation of PHIVAY.

1.4. Treatment of PLHIV

Three decades into the HIV pandemic, scientists have yet to find a treatment which is able to completely cure HIV infection. Luckily, we managed to develop interventions which are able to significantly improve health and survival rate of people living with HIV. In 1987, the first antiretroviral agent which proved to be effective against HIV, azidothymidine (AZT), was discovered and antiretroviral therapy (ART) was born. Since then, ART has seen many improvements. New antiretroviral agents and combinations of different antiretroviral agents have been discovered, resulting in the highly active antiretroviral therapy (HAART) we know today.

Current ART or HAART consist of multiple antiretroviral drugs, which are used in combination in order to maximally suppress viral replication. Combining different classes of antiretroviral drugs which act on different stages in the HIV replication cycle is also essential in order to prevent natural selection of mutated HIV particles with acquired resistance to one or more of the antiretroviral agents. If only one class of antiretroviral drugs were to be used, which was the case in the early years of ART, HIV strains resistant to the entire class of drugs can spread quickly and become dominant strains, which could lead to enormous challenges in treatment. Antiretroviral drugs are classified by the phase of the replication cycle they inhibit. For example, AZT is called a ‘Nucleoside reverse transcriptase inhibitor (NRTI)’, preventing the conversion of viral RNA to DNA so it cannot be inserted in the host DNA.

The WHO updated its guidelines on ART in 2015 and recommends a combination of two NRTI’s and one ARV from another class as the preferred first-line therapy for treatment initiation in adults, adolescents and older children (30). Besides superior efficacy and tolerability, this antiretroviral drug regimen has the advantage of being available as fixed dose combinations (FDC), which means that 3 different antiretroviral drugs are combined in a single
pill which has to be taken only once per day. This greatly increases the ease of use and results in better adherence to ART. The WHO also simplified its recommendations for initiating ART treatment. Instead of starting ART treatment in PLHIV the moment CD4+ T-cells in the blood dropped below a cut-off value (< 500 cells/mm³), with many exceptions for key populations, the WHO now recommends initiating ART from the moment a person is diagnosed with HIV (30).

Unfortunately, most newly infected people are not aware of their HIV-status in the early stages of the infection. HIV is commonly diagnosed by testing the blood (or saliva) for HIV specific antibodies, but it can take one to three months after infection took place before standard tests are able to detect them(31). More advanced tests can detect the presence of HIV in the blood 10 days after exposure, but are more expensive and only used as a confirmation of the diagnosis or in the context of therapeutic follow-up. Testing and diagnosis of HIV is the first step in the treatment cascade for HIV, also known as the HIV continuum of care. After confirmation of the diagnosis, PLHIV need to be referred to a health care provider in order to receive counseling about prevention and treatment. The next step in the treatment cascade is initiation of ART and retention of PLHIV in HIV care (32).

Once ARV medication is initiated, its effectiveness can be evaluated by monitoring the patients’ CD4+ T-cell count, which is the most important clinical indicator of the immune function and one of the strongest predictors of HIV progression. Healthy adults have an average CD4+ T-cell count between 500 cells/mm³ and 1600 cells/mm³. A CD4+ T-cell count lower than 200 cells/mm³ in PLHIV indicates progression to the third stage of HIV infection, AIDS. Another frequently used clinical indicator to determine whether or not there is a good response to the treatment is the viral load. The goal of ART is suppressing viral replication in the body, ideally to a level where the number of viral particles (copies) per ml is undetectable by lab tests. Indirectly, these indicators reflect how precise patients have been taking their medication, also known as adherence. Studies have proven that patients who suffer from chronic diseases, such as HIV, adhere poorly to their treatment recommendations, greatly reducing treatment effectiveness (33).

1.5. Adherence to ART

Adherence is commonly defined as ‘taking medications as prescribed by your health care provider’. The increasing prevalence and incidence of chronic diseases has urged the WHO to
broaden the definition of adherence to “the extent to which a person’s behavior - taking medication, following a diet, or executing lifestyle changes - corresponds with agreed recommendations from a health care provider” (34). This definition recognizes that adherence behavior can be influenced by various complex factors, rather than only medication related factors.

To achieve viral suppression, prevent the development of resistant strains, and reduce disease progression and death, high levels of adherence are necessary. Studies suggest that the minimum cut-off for sufficient ART adherence in order to achieve optimal outcomes ranges between 90% and 95% (35). One of the biggest challenges in research towards ART adherence is the lack of a ‘golden standard’ in the measurement of adherence. Frequently used indicators of adherence in current literature are self-reported adherence, CD4 + T-cell count and viral load.

Self-reported adherence is an inexpensive and simple method to measure adherence but is often an overestimation due to recall bias or to please the treatment provider and prevent criticism(36). This is particularly challenging in the pediatric population because the data refers to the child, but is provided by the caregiver. Another commonly used indicator for adherence is CD4+ T-cell count, which is the most important indicator of disease control and treatment effectiveness, reflecting the current status of the immune system in PLHIV. It is more expensive and not easy to measure, but is also more objective than self-reported adherence. Similarly, viral load, which is an indicator of viral replication, is also used as a measurement of adherence levels. These different methods of measuring adherence make it difficult to compare findings between adherence studies.

A meta-analysis of 82 ART adherence studies by Ortego et al (35) suggested that worldwide an estimated 62% of people reported >90% intake of prescribed ARV. Results did not vary significantly when comparing different cut-off values for adherence, the number of measurement methods used and the type of measurement methods used. Interestingly, the study found that in low-resource countries the average proportion of adherence is higher than in high-resource countries, although it must be taken in consideration that less than 15% of the studies was conducted in low-resource countries.

Similar regional differences were reported in a meta-analysis and systematic review by Kim et al (37) comparing ART adherence levels between HIV infected adolescents and youth (HIVAY) in Africa/Asia and Europe/North America. More than 70% of HIVAY in Africa and Asia indicated being adherent to ART compared to 50% of HIVAY in Europe and North
America. These meta-analyses on adherence suggest that worse treatment outcomes of PLHIV in SSA are not the result of lower levels of adherence, but are more likely the result of other differences such as access to health care, resources and epidemiology of HIV. When comparing adherence levels between HIV infected adults and HIVAY, significant lower levels of adherence were maintained in the HIVAY population and this difference was consistent for every region.

We can conclude that HIVAY are less likely to maintain adherence and to achieve viral suppression compared to HIV infected adults, no matter where they live. Several limitations should be considered when interpreting these findings. The methodological quality of the reported studies was low overall, and the lack of an accurate standardized measurement of adherence makes comparison difficult. It is also unknown how representative individuals who participate in adherence studies are of the general population from which they are drawn.

1.6. Challenges of ART adherence during adolescence

A recent study on retention of adolescents in ART programs in Uganda showed that after 2 years, the level of retention had decreased to 71%, with the risk of non-retention being significantly greater in older adolescents (15 – 19 years) compared to young adolescents (10 – 14 years) (38). A recent meta-analysis on the global adherence of adolescents even concluded that 40% of the adolescents that had initiated ART were non-adherent. They also found that the level of non-adherence was significantly higher with older adolescents (14-19 years) compared to young adolescents (10-14 years). This result is consistent with other studies investigating ART adherence in adolescents and children in a comparable setting (39).

Recent studies have demonstrated the highly unique challenges HIVAY face in maintaining ART adherence, which might provide an explanation for the lower rates of adherence compared to their adult counterparts(40). Adherence behavior in HIVAY is influenced by various psychosocial, socio-economical, treatment-related and individual factors, making it difficult to distinguish the individual contribution of a factor(41). Adolescence is commonly defined as the transitional stage in the human development between the start of puberty and the age of adulthood. While the age of adulthood is legally defined in most countries, the start of puberty is not and varies significantly between and in different regions. However, to create statistical consistency in literature, adolescence is commonly defined as those persons between the age of 10 and 19 years old.
Adolescents undergo mental, physical and emotional maturation which is characterized by behavioral experimentation, identity formation and heightened risk-taking behavior. Decisions and opinions concerning relationships, sexual behavior, alcohol and recreational drug use are often formed during this period. Additionally, adolescents are prone to peer pressure and sexual pressure, have limited access to health facilities and often lack knowledge and financial autonomy. Research has shown that knowledge about HIV prevention among HIVAY is low, and there is a trend toward adolescent males and females (15–19 years) having less knowledge than young adult males and females (20–24 years)(6). These psychosocial and drug-related challenges can compromise ART adherence as well as further development into adulthood (42).

While ART adherence in children is strongly dependent on the parent and/or caregiver and their relationship with the child, ART adherence in HIV infected adolescents is far more complex and has more influencing factors. The first challenge in this transition to adolescence is disclosure of their HIV status. There is evidence that disclosing the HIV-status to children yields health benefits (reduces death rates) while there is little evidence that it could cause psychological or emotional harm (43). The WHO suggests that children should be disclosed about their HIV-status at the age of 6 to 12 years, while younger children should be told their status “incrementally to accommodate their cognitive skills and emotional maturity, in preparation for full disclosure” (44).

Adolescents are viewed upon neither as children nor as adults, causing them to be an age group that is overlooked in many ways. In most non-industrialized countries, there is no specialized care for the adolescent age group. The absence of dedicated facilities and health care professionals for adolescents creates an important barrier for accessing health care facilities. It is often unclear whether the care of adolescents should be managed by pediatricians or adult physicians. Pediatricians are often hesitant to transfer their chronic care adolescent patients, with who they have a mutually trusting relationship has been built, to adult care facilities (45).

These findings suggest that adolescents could benefit greatly from interventions that support their adherence, as they gradually become more independent and parents/caregivers withdraw their supervision of their medication adherence.

A remarkable result from the meta-analysis by (37) is that African adolescents have adherence rates similar to those of their adult counterparts, and significantly higher than European or North-American adolescents. A possible explanation for this might be that access to ART is still one of the biggest limiting factors to adherence in SSA. It must also be taken in
consideration that the complexity in medication regimes greatly differs between SSA and industrialized countries, and thus confounding the difference in adherence rate.

When investigating possible barriers to access and ART adherence in resource limited settings, the most commonly cited were lack of knowledge of HIV status and treatment options, fear of stigma and discrimination, and poor access through lack of health care infrastructure and resources (39, 46, 47). The most important barrier that was reported was unintended disclosure of the HIV status. Adolescents often felt that they had to choose between taking their medication and keeping their HIV status a secret. Forgetfulness due to other preoccupations was also frequently mentioned as a barrier to adherence in recent studies (48). Facilitating factors include clinical youth support groups, support from family and health care providers, disease knowledge, self-motivation and perceived treatment outcomes (48, 49).

2. Possible interventions

2.1. ART adherence enhancing interventions

The numerous and valuable benefits of maintaining optimal ART adherence in PLHIV, have made it a priority target in research towards developing new interventions. These new interventions vary greatly in used approach, potential reach, resource intensiveness and on what level they apply (50). On one side of the spectrum you have interventions using a public health approach, applied at the level of policy makers and the health system itself. For example, expanding support services for PLHIV in epidemic areas. These interventions have maximum potential coverage but lack attention to the individual needs of the patients. They require the cooperation of policy-makers and the effects of the intervention are difficult to measure, but tend to be cost-effective. Interventions at the level of health providers and health facilities (eg. Hospitals, nurses) also have the potential to reach a great number of PLHIV, but can be adapted more easily to individual needs. An example of such an intervention is making hospitals youth friendly by making them accessible for HIVAY after school hours (51). On the other side of the spectrum there is the individualized approach to improve ART adherence in PLHIV. They can be targeted towards the patients themselves, for example education and individual counseling, but also towards the direct environment of the patient, such as family education. Due to the design of these interventions, focusing on individual needs of PLHIV, they are often resource intensive and have less coverage potential. The advantage however is that the effects
of these interventions can be studied more easily and if proven cost-effective, scaled up to increase coverage.

A wide range of interventions using an individualized approach in order to improve ART adherence have been identified. Some are based on underlying (behavior) theories, others target barriers to adherence unique to key populations (52). We have identified patient related barriers, treatment related barriers, socio-economic barriers, disease related barriers or barriers that are a combination(53). Some of the most frequently studied examples are patient counseling and education, provision of adherence support devices, peer support groups, medication regimen changes, directly observed therapy (DOT), financial incentives and last but not least, phone or text reminders (54, 55). Phone or text reminders are part of a promising new type of interventions using recent advancements in technology, such as online platforms or mobile phone applications, to potentially reach a big number of PLHIV, but still with an individualized approach (56). It is suggested that these interventions could prove particularly beneficial and effective in improving adherence in HIVAY, since adolescents and youth in general have rapidly adapted and become familiar with these new technologies (57).

While barriers and facilitators of adherence in HIVAY have been studied extensively over the last few years, research on interventions designed to improve ART adherence in HIVAY is very limited. A systematic review on interventions to improve the linkage, retention and adherence to ART in adolescents found that in a period of 13.5 years (2001 – 2014), only 11 studies that met the inclusion criteria were published (50). In only five of the 11 studies improving adherence in HIVAY was the main target. Interventions included counseling and education, peer support, provision of adherence support devices, financial incentives and DOT, all of which use an individual approach and are resource intensive. None of the studies included had more than 30 participants and with the exception of one study, they were conducted in high resource settings. A similar systematic review by Reisner et al. identified seven intervention studies targeting improved ART adherence amongst HIVAY. Interventions included counseling and education, regimen-related interventions, phone reminders and DOT(42). DOT means ARV medication is administered to patients by a health care practitioner. Studies using DOT as intervention reported that the positive effect on adherence diminished rapidly after the intervention ended, and no long-term benefits were observed (58). Studies using simplified ART regimens (one pill a day) and phone reminders suggested some improvement, but with 37 and 8 participants respectively, caution is needed when interpreting these results. Counseling and education based interventions showed most evidence for effectiveness, although these
results should be interpreted with caution since participant groups, settings and content of interventions varied considerably. Earlier this year, Reif et al. (51) published one the first intervention studies aiming to improve retention in the HIV treatment cascade among HIVAY at the level of health care providers. Implementation of a youth-friendly adolescent clinic for HIV care showed significant improvement in all measured outcomes by improving the proportion of patients enrolling in care and initiating ART (51).

In contrast to research targeted at improving adherence amongst adolescents, interventions to improve adults’ linkage, retention and adherence to ART have been studied intensively and some have been introduced into routine clinical practice (59). A recent review on adherence enhancing interventions included 49 randomized clinical trials, but reported that only 10 RCT’s successfully improved both adherence and clinical outcomes (56). They were unable to identify factors that would explain why some interventions were more successful than others. It is suggested that multicomponent strategies tend to be more effective in improving poor adherence (42). Some of the successful interventions included: individual patient counseling, a web based adherence behavior program, reduced frequency of medication, home visits by nurses combined with telephone support and directly observed therapy.

2.2. EHealth

Interventions using these recent technological advancements have great potential thanks to some unique features. The widespread use and availability of mobile phones and digital online platforms have made it possible to develop interventions tailored to individual needs which also have great coverage potential (60).

Recently, a systematic review identified 10 computer based adherence improving interventions and demonstrated the potential of computer based intervention(61). However, the reported studies all have methodological limitations inherent to the novelty of computer based interventions: small sample sizes, self-report as a sole measure of adherence, a short follow-up window, and lack of a control condition that equated for computer interaction time (61). Therefore, it is statistically unjustified to say that these interventions improve adherence significantly, but they show a lot of promise nonetheless.

In the last three decades, the use of computers and mobile phones has increased exponentially. The worldwide availability and use of these devices has created the possibility to use these new
technological advancements in all levels of health care. The term ‘eHealth’ refers to the use of information and communication technologies (ICT) for health (WHO definition), including treatment, conducting research, educating, tracking diseases and monitoring public health. Because of the broad definition of eHealth, sub-segment fields have emerged such as mHealth (mobile health), which is commonly referred to as the use of mobile communication devices for health services and information. As a result of this recent advancement in technology, eHealth and its possible applications are being studied increasingly and show promise on all levels of health care, including global health care (62). The rapid technological advancements in mobile phones over the last five years have also increasingly made the line thinner between mobile phones or mHealth and computers or eHealth. To this date, no standardized definition of mHealth has been established (60).

Not only the developed world has access to these technological advancements. In the last decade, low cost smartphones and internet cafés have allowed people in low income countries to increasingly find their way to text messaging and the internet (63). A study on the mobile phone use in 11 Sub-Saharan countries reported that an average of 53% owned a mobile phone, of which 25% reported being able to use it to browse the internet (64). Following this trend, interventions using mHealth systems in low-resource settings have been studied intensively over the last couple of years. Possible services that mobile technology can provide include educational and awareness programs, medication monitoring, disease tracking and other data collection services (60). A UNESCO report from 2013 found that SSA has the lowest literacy rates in the world, with 11 countries having adult and youth literacy rates less than 50%. The use of video and graphic content could be used to overcome that barrier and assist in mHealth or eHealth interventions (65).

Literature on the use of mHealth applications in the context of HIV care revealed a number of descriptive and (quasi-)experimental studies. A review of literature between 2001 and 2011 by Catalani et al. (32) showed that mHealth interventions can be useful at every stage in the HIV treatment cascade: from prevention to diagnosis, linkage to care, retention in care and ART adherence. The mHealth applications that were studied varied from text message reminders for appointments or medication to educational videos and adherence monitoring tools. At that time, literature on mHealth consisted mainly of small scale interventions, pilot projects and feasibility studies. The rapid innovation and the broad range of tools and initiatives as well as the lack of qualitative studies and trials have made it difficult to properly assess the effectiveness of eHealth interventions(66).
In the last five years, more compelling evidence for the effectiveness of mHealth interventions in improving ART adherence has been found. Two RCTs in Kenya investigated the use of mobile phone short message service (SMS) in improving adherence and both showed great promise (67-69). One RCT in Kenya by Lester et al. (68) investigated the effects of a mobile phone reminder intervention on adherence in adults, and showed significantly improved self-reported adherence rates and virological suppression in the intervention group compared to the control group. This effect was also seen in a RCT by Pop-Eleches (67) using a similar mobile phone intervention. A review by Horvath et al. (69) confirmed the effectiveness of mobile phone reminders and showed that both studies had a high level of evidence. This beneficial effect was not seen in a RCT by Shet et al. (70) investigating the effects of mobile phone reminders on adherence in Indian adults (18 – 60 years).

Literature on mHealth interventions to improve adherence among HIVAY is limited. Belzer et al. (71) conducted a pilot RCT study in 37 non-adherent HIVAY using mobile phone reminders and showed a significant improvement in the intervention group which persisted 12 months post-intervention. This effect was also seen in a pilot RCT study by Garofalo et al. (72) published earlier this year. Participants who received daily personalized text messages were 2.6 times as likely to report >90% adherence after 3 months compared to the control group. The effect of the intervention stagnated after 6 and 12 months, but remained significant compared to the control group (72). Both studies were conducted in the USA, and the majority of the 103 participants in the study by Garofalo et al. having a low socio-economic status, high levels of co-morbid substance use and mental health problems (72). Other previous intervention studies for HIVAY using mobile phone reminders had no control group in their design and other methodological limitations, but also suggest potential benefits. A possible explanation for the increased effectivity of mHealth interventions in HIVAY compared to adults is the fact that adolescents have shown to be early adaptors of these new technologies (57).

While mobile phone interventions have been increasingly researched over the last decade, research on internet and computer based interventions is still in its early stages. Computer and internet based interventions to improve adherence may be less feasible than mobile phone interventions in low resource settings such as SSA, due to much lower access to computers and internet compared to mobile phones (73, 74).

Computer based interventions try to improve ART adherence by changing the behavior of the patients using various different strategies or combinations (61). Approaches vary from improving HIV and ART related knowledge, to sending reminders, keeping track of
medications, providing peer support and other strategies targeting barriers to adherence. Computer based interventions can combine different strategies, targeting multiple factors that affect adherence at the same time. Further research will be needed in order to define cost-effectiveness, impact and usability for both mHealth and eHealth interventions.

2.3. Gaps in research

We can conclude that there is a significant discrepancy in the amount and quality of intervention studies aimed at improving ART adherence in adults compared to adolescents. One of the biggest gaps in current research is the lack of studies targeted specifically for the adolescent age group. Many studies either exclude adolescents from the inclusion criteria or do not differentiate between adolescents (10 -19 years), young adults (18 – 25 years), youth (15 – 24 years) or older adults, making it difficult to distinguish the effect for this highly unique population.

The lack of research on interventions addressing ART adherence in this already vulnerable group of young people living with HIV makes it difficult to design interventions on a bigger scale that are supported by evidence, that are cost-effective and sustainable. Therefore, rigorous evaluation of existing and new interventions applied at all levels of the health care system are recommended. Especially the biggest and most vulnerable group of HIVAY, living in Sub Sahara Africa could benefit greatly from tailored and high quality research on ART adherence interventions.

3. Objectives

3.1. Primary objective

The broad objective of this study is to improve adherence to HIV treatment among adolescents and youth living with HIV.

3.2. Secondary objectives

The qualitative study design will address two specific objectives. Identification of barriers to ART adherence in HIVAY and defining features and content that should be implemented on the digital platform.
The quasi-experimental design will evaluate the effectiveness of a pilot digital peer support system in improving HIV/ART knowledge, perceived importance of adherence, perceived self-efficacy in adhering and future intentions towards adherence. Possible predictors for adherence, such as age and gender, will be determined.

**Methods**

1. Study design

This study used a mixed methods design, which means we used several combined approaches. A cross-sectional design was used to generate base-line data. We extracted the information from adolescents and youth records from the comprehensive care clinic (CCC).

A qualitative design was used in order to collect qualitative data regarding barriers to maintaining adherence and the acceptability of a digital platform. Recommendations by HIVAY towards content and features that could be implemented in the digital platform intervention were also gathered. For this we conducted focus group discussions (FGD) and in-depth interviews with health care providers treating HIVAY (Key informant interviews, KII).

A quasi experimental design with pre-intervention and post-intervention comparison of data was used to determine the effectiveness of the eHealth intervention in improving ART adherence among HIVAY. The eHealth intervention used an online digital platform which was developed in conjunction with recommendations made by HIVAY in the FGD and aimed to improve adherence by providing peer support and improve HIV related knowledge.

2. Ethical considerations

The project received ethical and technical approval by the Kenya National Hospital and University of Nairobi Ethical and Research Review Committee (KNH/UON-ERRC) and NACOSTI, as well as approval by the Ghent University Hospital Ethics Committee. Participants were informed that the findings obtained from the study will be used to design health interventions in Kenya as well as globally. Informed consent, parental/guardian consent and ascent as appropriate was obtained from all participants before enrolling them in the study. The consent form was in English and Swahili. The consent was read aloud to the potential
respondents to overcome potential issues around illiteracy. They were told that participation is voluntary and they can stop at any time or refuse to answer any question.

3. Qualitative study

3.1. Participant recruitment

Participants for the FGD were recruited from HIVAY attending care at the Comprehensive Care Clinic and Family Care Clinic, both located at the Coast Provincial General Hospital (CPGH). CPGH is the second largest government hospital in Kenya and serves as the tertiary referral centre for the entire coast region. HIVAY that met the inclusion criteria were invited by youth coordinators who work with HIVAY at the clinics. A convenience sample of 24 participants were selected from 42 eligible HIVAY that accepted the invitations of the youth coordinators. Participants were divided in three groups of eight participants based on their age. The first focus group consisted of eight participants between 15 and 19 years old, the second focus group consisted of eight participants between 20 and 24 years old and the third group had four participants from both age groups.

Key informants were recruited from health care professionals involved in the treatment of HIVAY at both clinics. Two physicians and one youth coordinator that worked with HIVAY were asked and agreed to participate.

3.2. Intervention

A focus group discussion can be described as a group interview aiming to obtain opinions and ideas from key actors about a specific topic. In this study FGDs aimed to identify barriers for maintaining adherence in HIVAY and to define what content and features needed to be implemented in the digital peer support system, which would be based on recommendations made by the participants. The three FGD’s were conducted by ‘facilitators’, using a FGD interviewing guide to assure that the FGD’s were conducted correctly and that collected data could be compared between the different groups. Each FGD guide consisted of five open-end lead questions which assessed qualitative data such as perceived barriers to adherence. Secondary questions and probes were provided for the facilitators to steer the discussion for example when the responses on lead questions are limited or off-topic.
Key informant interviews (KII) aim to obtain opinions on a specific topic by health care providers or other professionals. This way we have different perspectives on the discussed topics. Two physicians and one youth coordinator were interviewed separately by trained research assistants. The interviewing guide for the FGD was also used for the KII.

3.3. Data collection and analysis

All qualitative data was audio-recorded and translated into English. Analysis of qualitative data was conducted using Nvivo version 11. The transcripts were read several times to identify all key ideas and themes. The next step was coding the data found in the transcripts based on the aims of the FGD. Emerging barriers to adherence were coded and assigned to various categories. Gaps in HIV/ART related knowledge were also coded and assigned. All emerged themes were compared between the three FGD’s as well as compared to results from the KII.

4. Quasi-experimental study

4.1. Participant recruitment

The sample of HIVAY involved in this study consists of HIV infected adolescents and youth, that are currently being treated with ARV and attending one of both HIV care clinics located at the Coast Provincial General Hospital (CPGH). CPGH is the second largest government hospital in Kenya and serves as the tertiary referral centre for the entire coast region. In order to be eligible to participate in this study, HIVAY needed to be between 15 and 24 years old and consent to participate must be given. For HIVAY below 18 years old, the consent of a parent or legal guardian was required as well. The participant information sheet and consent forms were translated from English to Swahili. Eligibility for the study was assured by study personnel, by asking the age of potential subjects and examining proof of HIV-infection. Documentation from the laboratory or hand written notes in the patient file from a person who did the HIV test were considered proof of positive HIV status.

92 participants were recruited and completed the pre-intervention questionnaire. 11 patients did not fill out the post-intervention questionnaire and were considered lost to follow-up. They were
excluded from the statistical analysis after establishing that the drop outs were at random and had no significant impact on the results.

4.2. Intervention

A secured website digital peer support system was developed in conjunction with HIVAY that was accessible by phone and computer. Participants were given a personal code by their health care provider that allowed them to access the website and create their own profile. The website combined information on HIV prevention, care and treatment, STI (sexually transmittable diseases) signs and symptoms, STI screening and treatment, safe sex, correct and consistent use of condoms, family planning services (contraceptive methods), alcohol and drugs, sexual and gender based violence, PMTCT etc. Furthermore, the website provided information on how to access health professionals for consultation/advice, additional health information and ART treatment adherence counseling services.

4.3. Data collection and outcome measurements

Data were collected from the participants using platform-delivered questionnaires at pre-intervention and after three months intervention. The questionnaire was not translated to Swahili after the FGD established that everyone in this age bracket has adequate understanding of English. The questionnaire consisted of several sections assessing various demographic, psychosocial and adherence behavior related variables. Demographic variables included gender and age. Psychosocial outcome measures included knowledge of HIV/ART, perceived importance of adherence, perceived self-efficacy in maintaining adherence and intentions to adhere in the next three months. The first section assessed participants’ knowledge of HIV and ART using 17 true/false items adapted from previously validated instruments with HIV-positive youth (76-78). A total knowledge score for each participant was calculated in SPSS, which represented the amount of correctly answered items. Possible scores ranged from 0 to 17, with higher scores on this measure indicating more accurate knowledge about HIV and ART.

The second section assessed the perceived importance of maintaining ART adherence by using eight items that rated the importance of critical adherence behaviors using a 5-point Likert scale adapted from Velasquez et al. (79) ranging from “Not important at all”(1) to “Extremely important”(5). A total score was calculated in SPSS, ranging from 0 to 8, with higher scores on
this measure indicating higher perceived importance of adherence. The Cronbach’s alpha of this scale was 0.778 pre intervention, suggesting good internal consistency.

The third section assessed the perceived self-efficacy using 17 items that rated participants’ confidence to perform critical adherence behaviors using a 5-point Likert scale ranging from “Not confident at all” (1) to “Extremely confident” (5), adapted from Velasquez et al. (79). A total score for self-efficacy was calculated using SPSS, with higher scores indicating more confidence in one’s ability to adhere to ARV. The Cronbach’s alpha of the used scale was 0.885 pre intervention.

The fourth section assessed participants’ intentions to perform adherence behaviors in the next three months using three items: taking medicines as prescribed by the doctor, taking medicines close to the right time every day, and not missing any doses. Responses were rated using a 5-point Likert scale ranging from “Not at all likely” (1) to “Definitely likely” (5). The Cronbach’s alpha was 0.549 pre intervention.

The fifth assessed the knowledge of their HIV-status using three items: “How did you get infected”, “How long have you lived with HIV”, “How old were you when you found out about your HIV status”. Outcome variables were respectively mode of infection, years lived with HIV and age of awareness of HIV status.

Adherence behavior outcomes were assessed using three items: “Are you currently on ARV?”, “How many doses have you missed last week?” and “Which reasons have led to missing your doses?”. In order to be eligible to participate in the study, ARV initiation was required. However, six respondents answered “no” the question in the questionnaire at baseline. If a participant indicated to have missed one or more doses in the last week, he was considered “not-adherent”, if no doses were missed, the participant was considered “adherent”. This was the only outcome variable measuring adherence used in this study.

The data was compiled and statistically analyzed using SPSS.

4.4. Data analysis

First, data was checked for inconsistencies and typographical errors, which were corrected. Before conducting any other statistical tests for data analysis, the distribution of the variables was checked for normality, using a Shapiro-Wilk test which is accurate in small samples. All variables showed a significant (p<0.001) difference when compared to the normal distribution. Non-parametrical tests had to be chosen for further statistical tests.
In order to compare paired categorical variables with a dichotomous distribution between pre- and post-intervention, for example the answers to the knowledge items (True/False), a McNemar test was conducted for each separate item. Ordinal paired variables for example variables measured on Likert scales, were compared between pre- and post-intervention using a Wilcoxon signed ranks test. This is also a non-parametrical test.

Besides the comparison of outcome measures between pre-and post-intervention, we also conducted a multivariate logistic regression analysis in order to determine whether or not adherence could be predicted based on independent variables such as age, gender and mode of infection. Results of this multivariate logistic regression analysis were not conclusive and different sets of predictors were found for adherence pre- and post-intervention. For these reasons, they were not included in the results section.

**Results**

1. Qualitative data

1.1. Focus group discussions (FGD)

1.1.1. Participant characteristics

Three FGD were conducted, each in a different age group. Each of the three groups consisted of eight HIVAY with mixed genders, that had initiated ART and attended clinics at the Coast Provincial Hospital. Participants in the first FGD were between 15 and 19 years old, in the second FGD ages were between 20 and 24 years old and in the third FGD ages were between 15 and 24 years old.

1.1.2. Barriers to ART adherence

During the FDG the participants were asked about the barriers to ART adherence. These answers were grouped into four categories: stigmatization linked to disclosure, gaps in knowledge, psychological barriers, health system related barriers.

*Fear for stigmatization due to disclosure*

“What I can say is that disclosure is the main issue”
A number of reasons were mentioned as responsible for participants’ inability to follow the treatment as scheduled, but fear for disclosure was mentioned most frequently as a barrier to adherence in all age groups. Whether it was frequent hospital visits, or taking medication in the presence of others, participants mentioned that they frequently did not adhere to their ARV regimens out of fear that it would raise suspicion and evoke questions that might lead to disclosure of their HIV status.

Participants that still attended school seemed encounter this problem more frequently. Both younger participants (15-19Y) that still attended boarding school and older participants (20-24Y) who attended high school or college mentioned this as a barrier to adherence.

“My problem is as a student if you have to keep leaving a class in session with a teacher to take your drugs, your friends will start to suspect and gossip about you, leading to your embarrassment. Also if your friend knows that you are on ARVs, s/he may decide to spread the news around especially when you are no longer friends”.

Having to take medication during school hours or skipping classes for doctor visits or medication refills was mentioned as a challenge to adherence by many of the participants. They feared that their peers would see them taking the medication and start asking questions. In other cases, they feared disclosing their status to the teacher. Considering that ARV regimens are often complex, consisting of at least three different medications which have to be taken at regular intervals, this barrier can also be interpreted as a ARV related barrier. Since ARV medication in low-resource countries is often distributed from hospitals or community centers, patients are required to frequent the hospital in order to get their medications refilled. From this perspective, it could even be considered a health care system related barrier.

“I can say that another challenge is for those that are in high school... let’s say colleges or high school. When it is their day to go pick drugs... the process of asking for permission from the teacher, telling her that you are sick... she gets to wonder, you fall sick every month...what is wrong with you. And at times when you say you are going to the hospital, they expect a letter from the doctor.”

“I went through boarding school. Most of the times my drugs used to be sent to school... When they arrive, the teacher calls me (mentions her name) come and take your drugs. So when you go with them to the dorm... you take them when you are in class, your classmates start wondering...this one takes drugs every day. At times you even over hear them discussing you ...what problem does (mentions her name) have? ...she should be
having a problem... so at times you even find it challenging to take the drugs because they will start talking”

Even if the hospital provided medication for several weeks, a participant feared that even a monthly hospital visits during school hours could create suspicion among his fellow students.

“It has some challenges because I have some friends at school... when I go to pick my drugs from the hospital and fail to go to school, they start asking me what I am suffering from that makes me be going to pick drugs every month.”

These data show that the desire to be socially accepted is a strong motivator for behavior in adolescents. Fear of not being accepted and stigmatized by their peers, resulted in missing doses of medication and/or appointments with health care providers.

The challenge of fear for disclosure was also mentioned by working participants. In order to have their prescriptions filled or get medical counseling, they have to ask their boss for a day off, which could be simply refused or lead to further questions.

“You are working at some place and when you ask your boss for a day-off, they refuse and for some reasons you cannot explain to them what you are feeling. This forces you to stop working and when you stay at home you are seen as an idler... so that is among the challenges we face ...this forces you to stay indoors ...coming out becomes a problem”

This example shows that fear of stigmatization due to disclosure acts not only as a barrier to adherence, but affects a wide range of psychosocial and economic outcomes in HIVAY. Fear of disclosure might be even more challenging in HIVAY that have relationships.

“I once had a girlfriend that I disclosed my status to. She did not believe what I said, so she went ahead to ask my friend if it was true. Now the friend went around telling people about it. I got so frustrated to an extent that I stopped taking drugs”

Fear from disclosing your status in a relationship is not only a potential barrier for ART adherence, at the same time it poses a risk for new infections. This was clearly illustrated by a participant from the youngest group (15-19Y).

“Okay, another challenge according to me is teenage affairs. I may have a boyfriend whom I love very much and would not want to lose. Even if I may want consider telling him my status but the fear of being rejected will deter me. We are advised to always carry our drugs just in case we may need to take them. But if the time to take drugs finds you at
your boyfriend’s place you won’t be able to take it. So this may go on so that every time you are at your boyfriend you don’t take your medication till you give up completely on it altogether”

The challenges that HIVAY face when it comes to disclosing one’s status in a relationship were also mentioned by participants from the older age group (20-24Y).

“When you have a fiancée, you are afraid that the moment you disclose to them they will leave you... so you keep hiding when taking those drugs.”

Whether it to is family, friends, employers, neighbors or even people they don’t know, almost every participant stated that fear of disclosing their HIV status was a barrier to ART adherence. The stigma that people living with HIV still experience is the main reason why they fear disclosing their status. This was mentioned frequently in all age groups.

“Because there are issues like stigmatization where a [HIV] negative person discriminates a HIV [positive] person for example by not wanting to shake hands or come close to them. I have experienced this before... “

“Another challenge is because of our age, when adults see us going to take drugs they start speaking behind our backs, others insult us, others ask, ‘how did someone this young get infected?’ This discourages a lot so that some people stop going for refilling.”

These quotes suggest that the stigmatization and resulting discrimination might be caused by the many misconceptions surrounding HIV infection that still exist among HIV negative people who are not infected. Both examples suggest limited knowledge on transmission of HIV among HIV negative people.

**Gaps in HIV and ART related knowledge as a barrier to adherence in HIVAY**

Unfortunately, these misconceptions on HIV related knowledge are not limited to the HIV negative population. The FGD showed that HIV and ART related knowledge among HIVAY showed gaps as well, even to the point where it could be considered a barrier to adherence.

Many of the participants had questions related to ARV medication itself, including side effects, regimen specific questions and practical problems such as lack of food at the time of the dose.
“For instance, maybe you take your drugs at six and you did not eat at lunch time and at night you have to wait until nine to eat. What will happen if you take those drugs before eating? Because I have a small brother who keeps on being told not to take his medication until he eats and at times food comes late. I do not understand.”

“Sometimes I will eat supper after I have taken the drugs. So in relation to nutrition, how many times am I supposed to eat? What are you supposed to eat?”

“Information regarding nutrition. Most of us adolescents and youths eat carelessly and as we are not informed on healthy eating and yet we may be using drugs. It would be good if we could get advice on this.”

Another perceived gap in knowledge among HIVAY was knowledge on transmission of STI’s such as HIV and how to prevent them. The amount of questions regarding HIV transmission was more than all than the amount of questions on other topics combined. Even in the group with HIVAY aged 20 to 24, there were many misconceptions on HIV transmission related topics which could be considered crucial knowledge for young people living with HIV.

“On sexual health, I would wish to know if I am having sex with my fiancée, how long can we have sex without using trust? I know that is one of the things youths need to know. Youths are supposed to know, if I am positive and my partner is negative... who gets hurt if we happen to have unprotected sex, is it both or one person? I have heard that, if you are HIV positive and the other person is negative and you indulge in unprotected sex, you end up infecting your partner and increasing your viral load and your CD4 count drops.”

“Let’s say I am giving birth... when I conceive. That time of giving birth, when I go to deliver, will the child come out positive or negative?”

“Information, for instance, about how we can stop spreading the infection. It is important because we have heard rumors that it is possible to have sex without protection and yet not transmit the infection to your partner. So we need to know how that is possible”

Another interesting gap in HIV related knowledge that emerged from the FGD was a lack of knowledge on psychological support and coping strategies for HIVAY. A participant from the youngest age group illustrated this nicely with the following quote:

“Information to help us deal with self-stigmatization because when one needs to accept their status and deal with the stigma so that they can open up to others. This information should help us accept ourselves”
Psychological burden of living with HIV

This was confirmed by a participant in the oldest age group and brings us to a third barrier for ART adherence identified in the FGD, the psychological burden of living with HIV.

“Youths should learn to accept themselves as they are. Not being in a position to accept your self is what leads to ignorance and poor adherence to medication. You should accept yourself as HIV positive. So just accept yourself, take your drugs and life will move forward.”

Furthermore, feelings of being an outsider or not being understood were mentioned by several participants as reasons for poor adherence to ART.

“I will talk about self-stigmatization. There are times as a youth or teenager one may wonder “Why am I the only one taking these drugs?” Maybe among your friends and family you are the only one taking drugs. That can discourage you to the point that you see no need of taking drugs.

HIVAY in SSA often face a number of biosocial and-economic challenges, such as financial problems, being responsible for the care of younger siblings, etc. which could add to perceiving ART adherence as less important.

“I had a big problem adhering to drugs because at that time I had a child, I broke up with the so called husband, (laughing) I was so stressed... I am a single mum then I see the burden of taking drugs daily.”

Health care system related barriers

Health care system related barriers were also mentioned by several adolescents. The lack of follow-up on adherence by health care providers was mentioned by one of the participants. He also feared disappointing his health care provider if would admit to have missed some doses.

“The doctor will not follow up on you to confirm if you finished the drugs (...) To make him happy you will just go there and tell him, yes they are finished or maybe you left them at home.”
Community Health Workers (CHW) who visit patients at home were also mentioned as a barrier for some adolescents. This can also be considered an example of fear for disclosure as a barrier to adherence because fear that neighbors will start asking questions and find out about their HIV status was their main concern.

The lack of youth specific health services and clinics was also mentioned by two adolescents. When going to an adult clinic for medication refills or an appointment, they sometimes felt judged by older patients “How can he or she be HIV+ at such a young age?”

1.2. Key informant interviews (KII)

1.2.1. Key Informant Characteristics

Three KII were conducted with health care professionals that are closely involved in the treatment of HIVAY. One youth coordinator and two physicians were recruited and interviewed. They all worked with HIVAY at the comprehensive care clinic from which the sample for the FGD was recruited.

1.2.2. Barriers to ART adherence

Disclosure

“Okay, the first challenge is disclosure”

Many similarities could be seen between self-perceived barriers to ART adherence discussed in the FDG and barriers perceived by the key informants (KI). Fear for disclosure of their HIV status was mentioned as the biggest challenge for HIVAY towards maintaining adherence in all three KII, although varying underlying reasons were given. Consistent with the FDG, fear of disclosing their HIV status towards friends and other members of their community because of potential stigmatization and other unwanted social consequences was mentioned.

“I think there are a lot of issues surrounding adherence concerning adolescents: from disclosure, to peer pressure, to stigma, to acceptability in the community, so all these things do impact the way adolescents adhere to their medication.”

“Yeah, disclosure being the main part and also stigma part among the community and also stigma among themselves.”
Interestingly, one of the KI identified disclosure of HIV status to the HIVAY him or herself, rather than disclosure towards others, as a barrier to adherence.

“Disclosure, for those who started on treatment at an early age. (...) Initially they were on treatment without knowing exactly what they are on and why they were taking them.”

“I think it’s varied, right from onset disclosure, disclosure issue is getting the patient to understand, without disclosure they will get problems with adherence because they don’t know why you are giving them drugs.”

Gaps in HIV and ART knowledge

Lack of understanding of disease and treatment was only mentioned in one KII as a specific barrier to adherence, but when asked about the perceived gaps in knowledge among HIVAY, many gaps were identified.

“But, the previous nine or ten years, the media has portrayed PLHIV as a very emaciated person who is coughing to death. And that is what the portrait which has stayed in most of our minds. (...) It needs to be portrayed in the right manner that HIV, yes it kills but if you are adhering to your medicines, if you are ready to take care of your nutrition and if you are ready to do your daily activities, you are not different than any other child”

Gaps in knowledge mentioned in the KII were similar to those in the FGD and included knowledge on MTCT and other modes of infection, nutrition related knowledge, knowledge on sexual and reproductive health, etc.

Medication and health care system related barriers were also mentioned with a lack of adolescent friendly clinics and other adolescent specific services being answered most frequently. Other barriers were similar to the ones mentioned in the FGD (Health care related barriers and non-adherence due to the psychological burden).
2. Quantitative data

2.1. Participant characteristics

Of the 81 participants that completed both questionnaires, 36 were male and had an average age of 17.9 (SD=2.3) years old. Female participants were slightly older, with an average age of 19 (SD=3.2) years old, but this difference was not found to be statistically significant. The mean age of all participants was 18.4 (SD=2.8) years, and ranged from 15 to 25 years old. Table 1 displays a summary of the participant characteristics.

<table>
<thead>
<tr>
<th>Gender</th>
<th>N (=81)</th>
<th>Mean age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>45</td>
<td>19.0 (3.2)</td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>18.4 (2.8)</td>
</tr>
</tbody>
</table>

Mother-to-child-transmission was mentioned most frequently as mode of infection, more specifically 44.4% (n=36) of the participants answered “MTCT” on the question “how did you get infected with HIV?”. “I don’t know” was answered by 28.8% (n=23) of the participants, while sexual contact and blood transfusion/organ transplant were stated as mode of transmission by respectively 11.1% and 13.6% of the participants. IDU and occupational exposure were each mentioned by one participant. We compared these data with the post intervention data, which showed some unexpected inconsistencies. We identified several possible reasons for this, which are discussed in the discussion section. Because of these inconsistencies, the results were not used in further analysis. Results are displayed in table 2.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Pre (N=81)</th>
<th>Post (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>How did you get infected with HIV?</td>
<td>I don't know</td>
<td>23 (28.4%)</td>
</tr>
<tr>
<td></td>
<td>MTCT</td>
<td>36 (44.4%)</td>
</tr>
<tr>
<td></td>
<td>Sexual Contact</td>
<td>9 (11.1%)</td>
</tr>
<tr>
<td></td>
<td>Injection Drug Use</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>Occupational Exposure</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>Blood Transfusion/Transplant</td>
<td>11 (13.6%)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>How many years have you lived with HIV?</td>
<td>11.4 (6.3)</td>
<td>13.5 (3.9)</td>
</tr>
</tbody>
</table>
How old were you when you learned about your HIV status?

<table>
<thead>
<tr>
<th></th>
<th>11,3 (6,0)</th>
<th>13,3 (4,2)</th>
</tr>
</thead>
</table>

2.2. Impact on adherence related psychosocial outcomes

2.2.1. HIV and ART adherence related knowledge

After conducting a Shapiro-Wilk test for the knowledge outcome scores both pre and post interval, we concluded that the scores are not distributed normally (p<0,01) and a non-parametrical test should be chosen to compare both samples.

A Wilcoxon signed ranks test (repeated measure paired sample t-test) was conducted and showed that participants did not have significant different knowledge scores pre intervention compared to post intervention (Z=-1,119, p =0,263).

In order to compare the proportion of correct answers for each question separately between pre- and post-intervention, we conducted an exact McNemar test (2 categorial dependent variables, 1 independent variable, 2 matched groups). We determined that there was a statistically significant difference in the proportion of participants who answered correctly on question 5 (p=0,027) “It is better to take a half dose of HIV medications than stopping the HIV combination medications completely.”, question 9 (p=0,039) “Recreational drugs and alcohol can affect the effectiveness of HIV medications.” and question 14 (p=0,049) “After a few months, it becomes less important to take HIV medications at the right time of day.”. Contrary to expectations, question 5 was significantly less correctly answered after the intervention compared to pre-intervention. Nearly half of the participants gave an incorrect answer post-intervention, compared to 35% (n=29) pre-intervention. We can conclude than the intervention had a positive effect on two knowledge items and a negative effect on one item. Total knowledge scores improved by 0,3 points, but this effect was not found to be statistically significant. Results are displayed in Table 3.

| TABLE 3: Frequencies of correctly answered knowledge items pre- and post- intervention |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Knowledge items                              | Pre (N=81)      | Post (N=81)     | McNemar         |
| Once the HIV viral load results are ‘undetectable’, HIV medications should be stopped | 67 (82,7%)      | 72 (88,9%)      | 0,332           |

35
If HIV medications are not taken at the right time of day, HIV drug resistance can occur.

HIV is cured when the HIV viral load blood test result is ‘undetectable’.

Condoms during sex are not needed when the HIV viral load blood test results are at ‘undetectable’ levels.

It is better to take a half dose of HIV medications than stopping the HIV combination medications completely.

HIV medications can cause unpleasant side effects (e.g., nausea, diarrhea, vomiting).

If sexual partners are both HIV-positive condoms are no longer needed.

Treatments are available to reduce HIV medication side effects.

Recreational drugs and alcohol can affect the effectiveness of HIV medications.

Providing HIV medications to a pregnant woman reduces the baby’s risk of being infected with HIV.

HIV medications can be taken at a different time of day on weekends or holidays.

It is best to stop HIV medications as soon as you feel better.

Missing a few doses of HIV pills can increase the amount of HIV virus in the body.

After a few months, it becomes less important to take HIV medications at the right time of day.

HIV medications help the body's immune system get stronger (CD4 increase).

When HIV medications work well, the HIV viral load increases.

Physical exercise can help reduce stress levels in HIV patients.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Pre</th>
<th>Post</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum knowledge score</td>
<td>13,7 (2,3)</td>
<td>14,0 (2,1)</td>
<td>0,263</td>
</tr>
</tbody>
</table>

2.2.2. Perceived importance in maintaining adherence

After conducting a Shapiro-Wilk test for the perceived importance scores both pre and post interval, we concluded that the scores are not distributed normally (p<0,01) and a non-parametrical test should be chosen. A Wilcoxon signed ranks test showed no significant
difference between total scores of perceived importance pre and post intervention ($Z=-0.466$, $p=0.641$) When comparing each item separately, no statistically significant differences were found for any of the items. An overview of the results is displayed in table 4.

<table>
<thead>
<tr>
<th>Psycho-social outcomes</th>
<th>Not important at all</th>
<th>Somewhat important</th>
<th>Important</th>
<th>Very important</th>
<th>Extremely important</th>
<th>Wilcoxon T values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking all drugs as prescribed by doctor</td>
<td>Pre</td>
<td>4 (4.9%)</td>
<td>1 (1.2%)</td>
<td>2 (2.5%)</td>
<td>0 (0.0%)</td>
<td>74 (91.4%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>2 (2.5%)</td>
<td>4 (4.9%)</td>
<td>3 (3.7%)</td>
<td>3 (3.7%)</td>
<td>69 (85.2%)</td>
</tr>
<tr>
<td>Taking drugs close to the right time every day</td>
<td>Pre</td>
<td>9 (11.1%)</td>
<td>0 (0%)</td>
<td>25 (30.9%)</td>
<td>1 (1.2%)</td>
<td>46 (56.8%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>6 (7.4%)</td>
<td>5 (6.2%)</td>
<td>24 (29.6%)</td>
<td>7 (8.6%)</td>
<td>39 (48.1%)</td>
</tr>
<tr>
<td>Taking drugs on time even if taking them in front of people who do not know you are HIV-positive</td>
<td>Pre</td>
<td>13 (16.0%)</td>
<td>4 (4.9%)</td>
<td>22 (27.2%)</td>
<td>2 (2.5%)</td>
<td>40 (49.4%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>17 (21.0%)</td>
<td>4 (4.9%)</td>
<td>16 (19.8%)</td>
<td>1 (1.2%)</td>
<td>43 (53.1%)</td>
</tr>
<tr>
<td>Taking drugs correctly even if busy at work, school, or at a party</td>
<td>Pre</td>
<td>1 (1.2%)</td>
<td>2 (2.5%)</td>
<td>7 (8.6%)</td>
<td>1 (1.2%)</td>
<td>70 (86.4%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>4 (4.9%)</td>
<td>0 (0%)</td>
<td>7 (8.6%)</td>
<td>1 (1.2%)</td>
<td>69 (85.2%)</td>
</tr>
<tr>
<td>Taking drugs correctly even if health has greatly improved</td>
<td>Pre</td>
<td>3 (3.7%)</td>
<td>2 (2.5%)</td>
<td>6 (7.4%)</td>
<td>1 (1.2%)</td>
<td>69 (85.2%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>0 (0%)</td>
<td>5 (6.2%)</td>
<td>4 (4.9%)</td>
<td>0 (0%)</td>
<td>72 (88.9%)</td>
</tr>
<tr>
<td>Taking drugs correctly even if feeling discouraged</td>
<td>Pre</td>
<td>3 (3.7%)</td>
<td>4 (4.9%)</td>
<td>5 (6.2%)</td>
<td>0 (0%)</td>
<td>69 (85.2%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>2 (2.5%)</td>
<td>3 (3.7%)</td>
<td>6 (7.4%)</td>
<td>2 (2.5%)</td>
<td>68 (84.0%)</td>
</tr>
<tr>
<td>Knowing latest CD4 value on lab report</td>
<td>Pre</td>
<td>5 (6.2%)</td>
<td>1 (1.2%)</td>
<td>12 (14.8%)</td>
<td>3 (3.7%)</td>
<td>60 (74.1%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>2 (2.5%)</td>
<td>1 (1.2%)</td>
<td>13 (16.0%)</td>
<td>3 (3.7%)</td>
<td>62 (76.5%)</td>
</tr>
<tr>
<td>Knowing latest viral load value on lab report</td>
<td>Pre</td>
<td>6 (7.4%)</td>
<td>2 (2.5%)</td>
<td>10 (12.3%)</td>
<td>5 (6.2%)</td>
<td>58 (71.6%)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>2 (2.5%)</td>
<td>1 (1.2%)</td>
<td>18 (22.2%)</td>
<td>5 (6.2%)</td>
<td>55 (67.9%)</td>
</tr>
</tbody>
</table>

2.3. Perceived self-efficacy in maintaining adherence

After conducting a Shapiro-Wilk test for the self-efficacy scores both pre and post interval, we concluded that the scores are not distributed normally ($p<0.01$) and a non-parametrical test should be chosen to compare both samples. A Wilcoxon signed ranks test showed no significant
effect on the total self-efficacy scores pre- and post-intervention (Z=-0.933, p=0.351). When comparing each question separately between pre- and post-intervention, no significant effect could be determined. Results are displayed in table 5.

<table>
<thead>
<tr>
<th>Psycho-social outcomes</th>
<th>Not confident at</th>
<th>Somewhat confident</th>
<th>Confident</th>
<th>Very confident</th>
<th>Extremely confident</th>
<th>Wilcoxon test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>t-values</td>
</tr>
<tr>
<td>Taking all drugs as prescribed by doctor</td>
<td>Pre 5 (6.2%)</td>
<td>2 (2.5%)</td>
<td>7 (8.6%)</td>
<td>0 (0.0%)</td>
<td>67 (82.7%)</td>
<td>0.256</td>
</tr>
<tr>
<td></td>
<td>Post 2 (2.5%)</td>
<td>1 (1.2%)</td>
<td>8 (9.9%)</td>
<td>0 (0.0%)</td>
<td>70 (86.4%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs close to the right time every day</td>
<td>Pre 9 (11.1%)</td>
<td>2 (2.5%)</td>
<td>21 (25.9%)</td>
<td>7 (8.6%)</td>
<td>42 (51.9%)</td>
<td>0.296</td>
</tr>
<tr>
<td></td>
<td>Post 5 (6.2%)</td>
<td>1 (1.2%)</td>
<td>25 (30.9%)</td>
<td>5 (6.2%)</td>
<td>45 (55.6%)</td>
<td></td>
</tr>
<tr>
<td>Making drugs a part of daily routine</td>
<td>Pre 9 (11.1%)</td>
<td>2 (2.5%)</td>
<td>9 (11.1%)</td>
<td>1 (1.2%)</td>
<td>60 (74.1%)</td>
<td>0.961</td>
</tr>
<tr>
<td></td>
<td>Post 7 (8.6%)</td>
<td>4 (4.9%)</td>
<td>11 (13.6%)</td>
<td>1 (1.2%)</td>
<td>58 (71.6%)</td>
<td></td>
</tr>
<tr>
<td>Keep taking drugs even when experiencing side effects</td>
<td>Pre 15 (18.5%)</td>
<td>4 (4.9%)</td>
<td>17 (21.0%)</td>
<td>1 (1.2%)</td>
<td>44 (54.3%)</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>Post 13 (16.0%)</td>
<td>4 (4.9%)</td>
<td>13 (16.0%)</td>
<td>3 (3.7%)</td>
<td>48 (59.3%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs on time even if they are HIV-</td>
<td>Pre 21 (25.9%)</td>
<td>1 (1.2%)</td>
<td>18 (22.2%)</td>
<td>4 (4.9%)</td>
<td>37 (45.7%)</td>
<td>0.459</td>
</tr>
<tr>
<td></td>
<td>Post 16 (19.8%)</td>
<td>2 (2.5%)</td>
<td>21 (25.9%)</td>
<td>3 (3.7%)</td>
<td>39 (48.1%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs on time even if daily routine is interrupted</td>
<td>Pre 6 (7.4%)</td>
<td>0 (0.0%)</td>
<td>12 (14.8%)</td>
<td>2 (2.5%)</td>
<td>61 (75.3%)</td>
<td>0.974</td>
</tr>
<tr>
<td></td>
<td>Post 5 (6.2%)</td>
<td>3 (3.7%)</td>
<td>10 (12.3%)</td>
<td>2 (2.5%)</td>
<td>61 (75.3%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs correctly even when not feeling well</td>
<td>Pre 6 (7.4%)</td>
<td>1 (1.2%)</td>
<td>6 (7.4%)</td>
<td>1 (1.2%)</td>
<td>67 (82.7%)</td>
<td>0.859</td>
</tr>
<tr>
<td></td>
<td>Post 6 (7.4%)</td>
<td>3 (3.7%)</td>
<td>5 (6.2%)</td>
<td>1 (1.2%)</td>
<td>66 (81.5%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs correctly even if it means disrupting eating habits</td>
<td>Pre 6 (7.4%)</td>
<td>1 (1.2%)</td>
<td>19 (23.5%)</td>
<td>1 (1.2%)</td>
<td>54 (66.7%)</td>
<td>0.359</td>
</tr>
<tr>
<td></td>
<td>Post 5 (6.2%)</td>
<td>0 (0.0%)</td>
<td>16 (19.8%)</td>
<td>2 (2.5%)</td>
<td>58 (71.6%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs correctly even if travelling away from home</td>
<td>Pre 3 (3.7%)</td>
<td>2 (2.5%)</td>
<td>7 (8.6%)</td>
<td>2 (2.5%)</td>
<td>67 (82.7%)</td>
<td>0.471</td>
</tr>
<tr>
<td></td>
<td>Post 5 (6.2%)</td>
<td>3 (3.7%)</td>
<td>5 (6.2%)</td>
<td>2 (2.5%)</td>
<td>66 (81.5%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs correctly even if busy at work, school, or at a party</td>
<td>Pre 4 (4.9%)</td>
<td>0 (0.0%)</td>
<td>11 (13.6%)</td>
<td>1 (1.2%)</td>
<td>65 (80.2%)</td>
<td>0.322</td>
</tr>
<tr>
<td></td>
<td>Post 3 (3.7%)</td>
<td>0 (0.0%)</td>
<td>8 (9.9%)</td>
<td>1 (1.2%)</td>
<td>69 (85.2%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs correctly even if health has greatly improved</td>
<td>Pre 3 (3.7%)</td>
<td>2 (2.5%)</td>
<td>7 (8.6%)</td>
<td>2 (2.5%)</td>
<td>67 (82.7%)</td>
<td>0.789</td>
</tr>
<tr>
<td></td>
<td>Post 4 (4.9%)</td>
<td>1 (1.2%)</td>
<td>8 (9.9%)</td>
<td>1 (1.2%)</td>
<td>67 (82.7%)</td>
<td></td>
</tr>
<tr>
<td>Taking drugs correctly even if feeling discouraged</td>
<td>Pre 5 (6.2%)</td>
<td>1 (1.2%)</td>
<td>11 (13.6%)</td>
<td>1 (1.2%)</td>
<td>63 (77.8%)</td>
<td>0.631</td>
</tr>
<tr>
<td></td>
<td>Post 4 (4.9%)</td>
<td>2 (2.5%)</td>
<td>10 (12.3%)</td>
<td>1 (1.2%)</td>
<td>64 (79.0%)</td>
<td></td>
</tr>
<tr>
<td>Discussing openly with doctor any problems related to drugs</td>
<td>Pre 7 (8.6%)</td>
<td>1 (1.2%)</td>
<td>6 (7.4%)</td>
<td>1 (1.2%)</td>
<td>66 (81.5%)</td>
<td>0.865</td>
</tr>
<tr>
<td></td>
<td>Post 8 (9.9%)</td>
<td>1 (1.2%)</td>
<td>5 (6.2%)</td>
<td>2 (2.5%)</td>
<td>65 (80.2%)</td>
<td></td>
</tr>
</tbody>
</table>
2.4. Intentions in maintaining adherence over the next three months

After conducting a Shapiro-Wilk test for the knowledge outcome scores both pre and post interval, we concluded that the scores are not distributed normally (p<0.01) and a non-parametrical test should be chosen to compare both samples. We compared scores pre-and post-intervention for each item, but no significant effect could be determined for any of the items. The p-value calculated for “Take drugs as close to the right time every day in the next three months” was 0.055, suggesting positive effects might become significant in bigger samples. Results are displayed in table 6. We compared total intention scores between pre-and post-intervention, but no significant effect could be determined (Z=1.684, p=0.092).

<table>
<thead>
<tr>
<th>Psychosocial outcomes</th>
<th>Not at all likely</th>
<th>'Not likely'</th>
<th>'Undecided'</th>
<th>'Likely'</th>
<th>'Definitely likely'</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take all drugs as prescribed by doctor in next 3 months</td>
<td>Pre</td>
<td>5 (6.2%)</td>
<td>2 (2.5%)</td>
<td>18 (22.2%)</td>
<td>51 (63.0%)</td>
<td>0.534</td>
</tr>
<tr>
<td>Post</td>
<td>2 (2.5%)</td>
<td>7 (8.6%)</td>
<td>0 (0.0%)</td>
<td>22 (27.2%)</td>
<td>50 (61.7%)</td>
<td></td>
</tr>
<tr>
<td>Take drugs as close to the right time every day in the</td>
<td>Pre</td>
<td>7 (8.6%)</td>
<td>14 (17.3%)</td>
<td>3 (3.7%)</td>
<td>26 (32.1%)</td>
<td>0.055</td>
</tr>
<tr>
<td>next 3 months</td>
<td>Post</td>
<td>1 (1.2%)</td>
<td>13 (16.0%)</td>
<td>4 (4.9%)</td>
<td>27 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Not miss doses of drugs in the next 3 months</td>
<td>Pre</td>
<td>10 (12.3%)</td>
<td>3 (3.7%)</td>
<td>12 (14.8%)</td>
<td>53 (65.4%)</td>
<td>0.428</td>
</tr>
<tr>
<td>Post</td>
<td>3 (3.7%)</td>
<td>6 (7.4%)</td>
<td>2 (2.5%)</td>
<td>20 (24.7%)</td>
<td>50 (61.7%)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 6: Intentions in maintaining ART adherence for each item separately
2.5. Impact on adherence related behavioral outcomes

At pre-intervention, the majority of participants reported excellent levels of adherence, more specifically 71,3% (n=57) reported not to have missed any doses in the last week. Post-intervention 78,8% (n=63) of the participants reported not to have missed any doses in the last week. After conducting a Wilcoxon signed ranks test, no significant difference could be determined (Z= -0,059, p=0,953).

For those participants who missed a medication dose, the following reasons emerged from their responses pre-intervention: ‘I forgot’ (25%); ‘I had no food’ (16,7%); ‘I was away from home’ (12,5%); ‘I ran out of pills’ (12,5%); ‘I was tired’ (4,2%) and ‘I fell asleep through dose time’ (4,2%). Similar frequencies were seen in the responses post-intervention. Results are displayed in table 7.

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Pre (N = 24)</th>
<th>Post (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>I forgot</td>
<td>6 (25,0%)</td>
<td>7 (33,3%)</td>
</tr>
<tr>
<td>I was busy</td>
<td>0 (0,0%)</td>
<td>3 (14,3%)</td>
</tr>
<tr>
<td>I had no food</td>
<td>4 (16,7%)</td>
<td>3 (14,3%)</td>
</tr>
<tr>
<td>I didn't want others to notice</td>
<td>0 (0,0%)</td>
<td>3 (14,3%)</td>
</tr>
<tr>
<td>To avoid side effects</td>
<td>4 (16,7%)</td>
<td>1 (4,8%)</td>
</tr>
<tr>
<td>I was away from home</td>
<td>3 (12,5%)</td>
<td>3 (14,3%)</td>
</tr>
<tr>
<td>I ran out of pills</td>
<td>3 (12,5%)</td>
<td>1 (4,8%)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>2 (8,3%)</td>
<td>0 (0,0%)</td>
</tr>
<tr>
<td>I was tired</td>
<td>1 (4,2%)</td>
<td>0 (0,0%)</td>
</tr>
<tr>
<td>I fell asleep through dose time</td>
<td>1 (4,2%)</td>
<td>0 (0,0%)</td>
</tr>
<tr>
<td>I felt OK</td>
<td>0 (0,0%)</td>
<td>0 (0,0%)</td>
</tr>
</tbody>
</table>

**Discussion**

This study examined barriers to ART adherence in HIV positive adolescents and youth, as well as the effects of an eHealth intervention on their adherence. Analysis of the emerged categories of barriers from the qualitative data revealed four categories: fear for stigmatization due to
disclosure, psychological burden, gaps in HIV/ART knowledge and health care/medication related barriers. These barriers were mentioned among all ages as well as in the KII, and are consistent with findings in similar studies (49). The perceived inevitability of stigma and discrimination if their HIV status would be disclosed was mentioned most frequently as a barrier to adherence and as a reason not to disclose to sexual partners and peers. A qualitative study by Mutumba et al. (80) concluded that “HIV stigma within home and school contexts and medication difficulties remain pertinent issues for adolescents living with HIV in Uganda”. The HIV positive adolescents in that study attributed stigma to the lack of knowledge or misconceptions about HIV, similar to results in this study. This was confirmed by results of the HIV stigma index for Kenya, which reported that half of respondents felt that the HIV related stigma and/or discrimination they have faced is due to people not understanding how HIV is transmitted and another 45% citing other people’s fears of infection by casual contact as the main reason. Participants in our study also mentioned discrimination due to fear of infection by giving a hand or sitting next to a HIV positive person.

Interestingly, barriers that emerged from the qualitative study were rarely mentioned as a reason for missing a dose in the quasi-experimental study results. Forgetfulness was by far the most mentioned reason for missing a dose, both pre- and post-intervention. ‘Not wanting others to notice’ was answered by none of the participants before the intervention and by three after the intervention. Forgetfulness as a major contributor to non-adherence was suggested in previous research, confirming our findings (45, 48).

The results of the quasi-experimental study suggest limited effects of the short term use of a digital platform on both psychosocial and behavioral outcomes. Total scores for knowledge, perceived importance of adherence, perceived self-efficacy and intentions to adhere in the future showed no significant difference after three months of intervention. Comparison of pre- and post-intervention results for each of the items separately showed that two statements were answered significantly better after the intervention. These statements were ‘recreational drugs and alcohol can affect the effectiveness of ART’ and ‘After a few months it becomes less important to take HIV medications at the right time of the day’, to which the correct answers are ‘true’ and ‘false’ respectively. These results suggest that the intervention corrected misconceptions surrounding the effects of recreational drug and alcohol use on ART and importance of maintaining adherence. One statement on HIV/ART knowledge was answered correctly significantly less after the intervention. ‘It is better to take half a dose of HIV medications than stopping the HIV medication combination completely’, to which the correct
answer is false. Before the intervention it was answered correctly by 64.2% of the participants compared to 50% after the intervention. This suggests that knowledge on HIV resistance to medication is limited in HIVAY and the intervention might have reinforced these misconceptions surrounding HIV resistance. A similar study using a web-based training program to enhance ART adherence among HIV-positive youth reported a significant increase in knowledge on HIV/ART, in self-efficacy and perceived importance of adhering to ART (78). This pilot study was conducted in the USA and involved 10 participants, eight of which were female. The difference in study sample and area might provide an explanation for the varying results between both studies.

Other findings in the quasi-experimental study confirm these gaps in knowledge on HIV. When comparing results of the perceived mode of infection and other HIV status related variables, we noticed some unexpected inconsistencies. Before the intervention, only one participant answered that injected drug use was the mode of infection compared to five participants after. Similarly, three more participants didn’t know how they got infected after the intervention, and five participants that answered MTCT before the intervention, answered other modes of infection after the intervention. These inconsistencies were also seen in the questions “How long have you lived with HIV” and “How old were you when you learned about your HIV status?”. Possible explanations for these results could be that HIVAY either gained more insights about their HIV status through the intervention, that they did not trust the security of the digital platform at the start of the intervention, thus giving answers that are more socially accepted or that they did not understand some of the questions. While it was established in the FGD that HIVAY attending care at the clinics would have sufficient knowledge of English to understand the questionnaires, this might have been overestimated.

The effect of the intervention on adherence behavior outcomes was found not to be significant either. The proportion of participants that reported perfect adherence in the last week did show a positive trend after the intervention, although changes might have been too small to be statistically significant.

Interpretation of the findings is subject to some limitations. Both the qualitative and the quasi-experimental study recruited a convenience sample from HIVAY attending HIV care at the second largest hospital of Kenya, located in the capital and one of the few that has clinics providing specialized HIV care for youth. As such, respondents might have not been representative for HIVAY living in rural and more remote areas who do not have access to such
facilities. Both the barriers they experienced in adhering to ART as well as psychosocial outcomes might be different.

Other limitations of the qualitative study include a lack of open-end questions towards participants’ opinion on facilitators of adherence, social support and awareness of their own status. It could be interesting to identify which members of their household or social network they have disclosed their status to, and what impact was. Recording socio-demographic characteristics of the participants such as education, household, parents’ HIV status and income might have been valuable as well.

Limitations of the quasi-experimental study Due to financial and logistical limitations, only three months of intervention could be completed, and no further follow up of the samples was conducted. Longer trials might be necessary in order to provide compelling evidence of effectiveness and follow up of the samples to determine long-term effectiveness. A pilot RCT of a computer-delivered intervention to facilitate adherence in HIVAY initiating ART showed that effects of the intervention were stronger at six months intervention compared to three months intervention, suggesting that the effect of such an intervention might be delayed or gradually improves over the duration of the intervention (81). In order to establish the effectiveness of this intervention, a control group might be needed.

Self-reported adherence as the only outcome measurement of adherence is susceptible to bias, and tends to be an overestimate of the reality. Addition of objective (clinical) parameters of adherence, for example CD4 cell count and HIV RNA copy concentrations, should be considered in future research in order to confirm self-reported adherence levels.

Participants that were lost to follow up might have had an impact on the significance of the findings as well as non-logical answers. 12% of participants who enrolled in the study and completed the pre-intervention questionnaire were lost to follow up at the post-intervention questionnaire, and were excluded from the results. When checking the credibility of the answers provided by the participants between baseline and after three months of intervention, several sections stood out by high rates of non-logical answers. For example, when asked what their current ART status was, 6 respondents answered in the pre-intervention questionnaire that they were not on ART at that moment, while this was an exclusion criterion for the study.

Several recommendations for future research data could be established. It could prove valuable to include data on the level of utilization in order to determine the impact of participant interaction with the digital platform on the overall effects of the intervention. Improving the
software for the digital platform to include registration of hours spend on the digital platform, video’s watched, posts read, interactions with peers and health care providers, etc, will allow future research to determine effects of the intervention based on actual participation. In our study, no data were collected on the participants’ level of utilization, but financial incentives were provided to ensure participant engagement. Some suggestions that emerged from the FDG including a secured personal page to monitor their personal treatment progress were not implemented in the digital platform due to technical difficulties. It might be useful to add more ART regimen related outcome data such as “are you responsible for your own medication adherence?”, the complexity of the ARV regimen, the current length of their treatment, etc. Other participant characteristics that might be meaningful in this research area are socio-economic data such as level of education, level of parents’ education, HIV status parents, income, etc. Future research could also benefit from an approach that makes distinction between behaviorally infected and perinatally infected HIVAY.

The impact of the timing on the effectiveness of the intervention might also be an interesting area of research. Interventions during critical periods for adherence, for example when starting ART or shortly after the onset of adherence problems, might have significant better effects on long-term outcomes.

**Conclusion**

Given the lack of evidence based intervention studies for improving adherence in HIVAY that live in resource limited settings, this study provides valuable information that supports further research in this area. To our knowledge, this was the first intervention study aiming to improve ART adherence for HIVAY using an online peer support platform in a low-resource setting. As access to internet and smartphones in resource limited settings is growing, these types of interventions hold great potential and warrant further research.
References


34. Toomey TL. ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION. WHO. Journal of medical Internet research.


Appendix A: FGD Interviewing guide

Adolescents and youth taking control of their HIV treatment issues, the case of Mombasa, Kenya (The ELIMIKA Project)

<table>
<thead>
<tr>
<th>Focus Group Identification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name/Initials of Facilitator</td>
<td></td>
</tr>
<tr>
<td>Name/Initials of Note taker</td>
<td></td>
</tr>
<tr>
<td>Date of Focus Group (dd/mm/yyyy)</td>
<td></td>
</tr>
<tr>
<td>Start Time (00:00 am/pm)</td>
<td></td>
</tr>
<tr>
<td>Stop Time (00:00 am/pm)</td>
<td></td>
</tr>
<tr>
<td>Tape Check Performed by</td>
<td></td>
</tr>
<tr>
<td>Transcriber</td>
<td></td>
</tr>
<tr>
<td>Transcription Date (dd/mm/yyyy)</td>
<td></td>
</tr>
</tbody>
</table>

[Note to facilitators: For the optimal use of this tool it is important to read through the tool carefully and prepare all the equipment required (i.e. index cards, markers, flipcharts etc.) prior to the start of the focus group discussion. Conducting this focus group well will yield results which are core to the success of the overall project]

**Introduction and Description of Project**

Hello and thank you for agreeing to participate in this focus group discussion. My name is ________________, and I am the facilitator for this group. [Introduce colleagues, note-takers, etc].

The purpose of a focus group discussion is to get inputs, ideas and opinions from key people on a topic. Today, we are discussing HIV therapy adherence among other sexual and reproductive health issues in adolescents and youths. We will mainly concentrate on factors influencing adherence and possibilities of using technology to improve it. We will seek your input regarding how such technological intervention may be designed and implemented in order to improve adherence. The discussion will last approximately one and a half hours.
Interview Guide

[Note to facilitators: assure participants of confidentiality; make sure that what is being shared will not leave the room]

<table>
<thead>
<tr>
<th>LEAD QUESTIONS</th>
<th>SECONDARY QUESTIONS AND PROBES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What challenges are adolescents and youths faced with in regards to adhering to HIV treatment?</td>
<td>Maybe start with question: is adhering to treatment easy for you or not? Be sure to discuss this in the context of: 1. HIV treatment 2. Sexuality and sexual health 3. Relationships? 4. Reproductive Health</td>
</tr>
<tr>
<td>[Note responses down on flip chart paper visible to the whole group. Responses may be discussed among the group, especially if there is disagreement]</td>
<td></td>
</tr>
<tr>
<td>2. What kind of information do you think/know HIV infected adolescents and youths need to have?</td>
<td>If not mentioned, find out suitability of a web-based digital peer support system i.e. 1. Find out about smart phone ownership 2. Find out about level of education 3. Find out about the easiest language to use on the website</td>
</tr>
<tr>
<td>[Note responses down on flip chart paper visible to the whole group. Responses may be discussed among the group, especially if there is disagreement]</td>
<td></td>
</tr>
<tr>
<td>3. What means of communication would best present the information discussed before in order to benefit HIV infected adolescents and youths?</td>
<td>Probe about what such name one would give such a web site? Probe for suitability of:  - Secured section to access own treatment data  - Live chat sessions with doctors  - Possibility to post questions  - Information on treatment, sexuality, reproductive health  - Games  - Discussion forum  - Chats  - (Video) blogs  - Treatment reminders</td>
</tr>
<tr>
<td>[Note responses down on flip chart paper visible to the whole group. Responses may be discussed among the group, especially if there is disagreement]</td>
<td>What other features would they think of? Ask if someone would be willing to contribute through blogging/vlogging/…</td>
</tr>
<tr>
<td>4. If a web-based digital peer support system were used to present the information, what features would you like included in the website?</td>
<td></td>
</tr>
</tbody>
</table>
5. What might we need to consider so as to have successful implementation of a web-based digital peer support system for improvement of HIV treatment adherence?

[Note responses down on flipchart paper visible to the whole group. Responses may be discussed among the group, especially if there is disagreement]

Be sure to get opinions about how a web-based digital peer support system would be accessible to:
1. Those without smart phones,
2. Those who are not tech-savvy,
3. Those that without computer access
4. Those in sessions at schools where use of phones is not allowed

This is the end of the focus group discussion. Thank you so much for sharing your ideas with us. Do you have any questions, or is there anything that you would like to add before we end?

If you have further thoughts about any of the issues we discussed today, please call Prof. Peter Gichangi, the study Site Principal Investigator at (041) 249 4866 or 0722 521 946.