7-18-2024

Optimizing Adherence to Antiretroviral Therapy among Adolescents Living with HIV in Low and Middle-Income Settings

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By

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A dissertation presented to the Brown School of Washington University in St. Louis in partial fulfillment of the requirements for the degree of Doctor of Philosophy

August 2024

St. Louis, Missouri

Dedication

This dissertation is dedicated to the loving memory of my mother, the late Olivia Nakafeero, who endured so much to ensure that I completed school.

Acknowledgments

I am deeply grateful to the many individuals who have supported and guided me throughout my doctoral program. Their unwavering commitment and contributions have been crucial to my doctoral journey. First and foremost, I express my utmost gratitude to Professor Fred Ssewamala, my dissertation chair and mentor. His dedication and countless hours of guidance have not only shaped me into a better scholar but have also significantly influenced my personal and professional growth. Your advice has been instrumental in making this journey smooth. I am also thankful to you for opening the doors of the International Center for Child Health and Development (ICHAD) and allowing me to be a graduate research associate. The resources and data provided by ICHAD have been crucial in writing my dissertation. I hope the results from this dissertation contribute to the ICHAD research agenda.

I would also like to extend my gratitude to the other dissertation committee members, including Drs. Ross Brownson, Mary McKay, Kim Johnson, Proscovia Nabunya, and Torsten B. Neilands. Their collective support and extensive feedback on my area statement, proposal, and dissertation have not only strengthened my research but also significantly shaped me into a better researcher. I am grateful for their dedicated time to my academic growth.

The generous support of the McDonnell International Scholars' Academy made my doctoral studies possible. Additionally, I would like to acknowledge the National Institute of Child Health and Development for funding the Suubi+Adherence study (PI: Ssewamala), which provided the data used in this dissertation.

I extend my appreciation to the directors, staff, and fellow graduate research associates at the ICHAD office at the Brown School. Your support has made the journey much more enjoyable. I also want to express my gratitude to the ICHAD Uganda team members who

dedicated countless hours to ensuring the success of the Suubi+Adherence study, making this dissertation possible. I am also grateful to the 702 adolescents and their caregivers who participated in the study.

At the Brown school, I would like to thank the program director, Dr. Patrick Fowler, and the program manager, Jennifer Ramirez, and here predecessors, including Smriti, and Megan for their leadership in the doctoral program. I am also grateful to Hannah, Olivia, Mustafa, Yadi, Woodjerry, Dennis, and our entire cohort. You were incredible. A special thanks goes to Dr. Josephine Nabayinda, my close friend, fellow graduate student at the Brown School, and research associate at ICHAD. Throughout the PhD journey, you have been an endless source of support. I appreciate your consistent encouragement, a keen eye for detail, and willingness to review every document that I shared with you.

I must also express my appreciation to my wife, Dorothy. Your unwavering support and reminders about maintaining a healthy work-life balance have been essential. I am grateful for your patience during my sleepless nights and for understanding the sacrifices I made to concentrate on my dissertation. To my son, Kelsey, knowing that you were always watching was a constant motivation and a source of joy. Your occasional distractions from work have reminded me to take much-needed breaks.

Finally, I want to acknowledge my father, Mr. Nsubuga Samuel, my late mother, Olive Nsubuga, and my siblings, Alice, Godfrey, and Fred. I am forever grateful for the sacrifices you made to ensure that I had the opportunity to pursue my education. Your belief in me has been a driving force throughout this journey. Your sacrifices were not in vain, and I am eternally grateful.

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Abstract

Optimizing Adherence to Antiretroviral Therapy among Adolescents Living with HIV in Low and Middle-Income Settings

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Doctor of Philosophy in Public Health Sciences,

Washington University in St. Louis, 2024

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Globally, 1.8 million adolescents are living with HIV (ALHIV), of whom 89% (1.5 million) are in Sub-Saharan Africa (SSA) (UNAIDS, 2021b). Unfortunately, despite advances in prevention—such as the prevention of mother to child transmission (PMTCT) and pre-exposure prophylaxis—new infections continue to occur. For example, in 2021 alone, the number of new HIV infections among adolescents aged 10 to 19 was 160,000 cases. Moreover, the rate of HIV-related deaths among adolescents has only declined by 10% in the last decade, which is not fast enough to meet the 2030 global targets. Despite antiretroviral therapy (ART) playing a crucial role in controlling HIV, ALHIV have poor ART adherence and subsequently face low levels of viral suppression, which calls for more efforts towards reversing the trends among ALHIV. However, the ALHIV (10 – 19 year) have received less attention, evidenced by the relatively limited research on interventions to improve outcomes in this group.

Guided by a combination of behavioral theories, including asset theory, health belief model, and the socioecological model, this dissertation addressed three research aims. ***First***, the dissertation aimed to compare the performance of three adherence measures —self-reports, pill

counts, and electronic adherence measured using Wisepill devices—in monitoring ART adherence and predicting viral suppression (Aim 1). ***Secondly***, it aimed to develop and validate a model to predict the risk of virologic failures (Aim 2). ***Finally***, this dissertation aimed to examine the pathways through which addressing household economic insecurity using an economic empowerment intervention might influence ART adherence among ALHIV in Uganda by assessing the mediating effects of adolescent social transition, barriers to medical care, and adherence self-efficacy.

The dissertation used data from 702 ALHIV enrolled in a National Institutes of Health-funded longitudinal two-group (1:1) cluster-randomized clinical trial, the *Suubi+Adherence* study (R01HD074949) that tested the impact of an economic empowerment (EE) intervention—comprising incentivized youth savings accounts, financial literacy training, and micro-enterprise workshops—among ALHIV in Uganda. To be eligible, participants had to meet the following criteria 1) aged 10 to 16 years; 2) received medical confirmation of their HIV-positive status; 3) awareness of their HIV status; 4) living within a family setting, as opposed to institutionalized care where distinctive characteristics and requirements may vary; 5) being registered and receiving antiretroviral therapy (ART) from one of the selected collaborating clinics involved in the study.

To address **Aim 1**, baseline data from the *Suubi+adherence* study was used. To begin, the performance of the three adherence measures (self-reports, pill counts, and Wisepill) was compared using the Kappa and agreement coefficient statistics to determine their concordance. This was followed by the Bland-Altman analysis to determine the bias between the measures. In addition, the sensitivity, specificity, and area under the receiver-operator characteristic (ROC) curve were determined for each adherence measure to ascertain how accurately the adherence

measures predicted viral suppression (<200 copies/mL). Finally, separate covariate-adjusted multilevel logistic regression models were fitted to determine the association between each adherence measure and viral suppression. **Aim 2** relied on baseline data, as well. Specifically, for this aim (2), guided by theory, I used selected sociodemographic, behavioral, psychological, economic, and treatment-related factors to develop and validate a model to predict virologic failure (defined as having a viral load of ≥ 200 copies/mL. Least absolute shrinkage and selection operator (Lasso) regression using 10-fold cross-validation with bootstrapping was used to select the predictors for the final model. Model performance was assessed by determining the discrimination using the c-statistic and calibration by drawing a calibration plot. To address **Aim 3**, longitudinal data collected at 3 time points—baseline, and years six and seven post intervention initiation—was used to determine the long-term direct and indirect effects of the EE intervention on ART adherence. Sequential mediation via structural equation modeling in *Mplus* software was used to address Aim 3.

Results from self-reported adherence under **Aim 1** indicate that at baseline 73% of ALHIV reported good ART Adherence—defined as adherence ≥90% (Byrd et al., 2019; Ministry of Health, 2022). At the same measurement point (baseline), 67.1% reported virological suppression. Taken as a whole, these results point to poor adherence by ALHIV who were enrolled in *Suubi+Adherence* at baseline. There was considerable disagreement between the adherence measures employed, which were: self-reports, pill counts, and electronic adherence using Wisepill devices, with kappa values below 0.10 and covariate-adjusted AUC slightly above 0.60. When compared, the three adherence measures exhibited more disagreement when the mean adherence was low, but the agreement improved with increasing mean

adherence. Only self-reported adherence had a significant relationship with viral suppression, OR = 2.16 (95% CI: 1.25 – 3.81), p = 0.006.

Regarding the risk prediction model **(Aim 2)**, a model with 24 predictors was developed using a lambda value of 0.0071304. Variables retained in the model included participants' age, sex, work status, stigma, depressive symptoms, adherence self-efficacy, HIV knowledge, duration with HIV, time spent on ART, communication with the caregiver, family cohesion, social support, orphanhood status, number of people in the household, HIV disclosure, years spent at the current residence, and household asset ownership. The model predicted virologic failure with an AUC of 73.8 (95% CI: 68.3 – 78.0) and an almost perfect calibration of 0.985.

Finally, in **Aim 3**, the results showed a significant direct effect of the intervention on ART adherence was observed, $\beta = 0.066$ (0.007, 0.125), $p = 0.028$. In addition, the intervention had a significant total indirect effect on ART adherence, $\beta = -0.028$ (-0.054, -0.002), $p = 0.033$. A closer examination of the pathways revealed that the indirect effect was mediated through barriers to medical care, $\beta = -0.030$ (-0.057, -0.004), $p = 0.026$. Specifically, the intervention was efficacious in reducing the barriers to medical care, $\beta = -0.178$ (-0.259, -0.096), $p < 0.001$. However, paradoxically, participants experiencing more barriers to medical care also reported higher levels of ART adherence, $\beta = 0.170$ (0.036, 0.304), $p = 0.013$.

Overall, this dissertation adds to our understanding of the challenges and the strategies to enhance ART adherence and viral suppression among ALHIV in Uganda and similar low-resourced high-HIV burden settings. In summary, self-reported adherence was found to significantly predict viral suppression. In addition, a model that can accurately predict the risk of virologic failure among ALHIV was developed using the participant's socioeconomic, behavioral, psychological, and economic information. More importantly, the dissertation showed

that providing the ALHIV and their families with financial resources through a family economic empowerment intervention improved their ART adherence and highlighted alternative pathways influencing this relationship. These findings point to a pressing need for more efforts to improve ART adherence among ALHIV and the need to incorporate interventions that address poverty in the programs aimed at controlling HIV.

Chapter 1: Introduction

Background and significance.

The global HIV/AIDS epidemic continues to be a significant public health challenge, with a disproportionately high burden of the disease in low-resource settings. Among the populations most affected, adolescents represent a particularly vulnerable group. Recent UNAIDS statistics show that there are a staggering 1.8 million adolescents living with HIV (ALHIV), of whom 89% (1.5 million) are in the Sub-Saharan Africa (SSA) (UNAIDS, 2021b). This highlights the disproportionate burden of the disease in this region, and among adolescents. In 2021 alone, 160,000 adolescents aged 10 to 19 became infected with HIV (UNAIDS, 2022a). These new infections accounted for 11% of the total new HIV infections reported during that period. Additionally, over 30,000 adolescents within the same age range lost their lives due to HIV-related causes (UNICEF, July 2021). What makes the situation even more concerning is that the rate of HIV-related deaths among adolescents have only declined by 10% in the last decade, compared to adults and children below 10 years, in whom the HIV-related deaths have drastically declined by over 64% and 74%, respectively (UNAIDS, 2021b). On a positive note, UNICEF data showed that the incidence of HIV in adolescents in the Eastern and Southern Africa sub-regions has reduced by 41% since 2010 (UNICEF, July 2021). Unfortunately, this rate of decline is not fast enough to meet the 2030 global targets, which calls for more efforts towards ALHIV in the region.

Poor adolescent ART adherence

One of the most important breakthroughs in fighting HIV was the discovery of antiretroviral therapy (ART). However, successful management of HIV/AIDS is largely contingent on sustained ART adherence. To realize the benefits of ART, adolescents must adhere

to ART at least 95% of the time (Byrd et al., 2019). Poor adherence often leads to sub-optimal drug concentrations, providing an opportunity for the virus to multiply and ALHIV to develop virological failure. *Virological failure*—characterized by uncontrolled viral replication despite ongoing treatment—can lead to disease progression, the development of drug-resistant strains, and enhanced transmission risks. Unfortunately, ALHIV have poor ART adherence and low levels of viral suppression. For example, a systematic review and meta-analysis including 72 studies with >50,000 children below 18 years in low and Middle-Income Countries (LMICs) found that only 72% of these children and adolescents achieved viral suppression (Boerma et al., 2016). In another systematic review of 12 studies with over 4400 ALHIV in SSA, Mengesha et al., (2023) found the ART adherence rates to be at 73% (Mengesha et al., 2023). Similar adherence levels have been reported in Uganda—the site of the proposed dissertation (Samuel Kizito et al., 2022).

Optimizing ART adherence measures in adolescents.

To better understand ART adherence, accurate and reliable measures are crucial, yet to date, there is no universally acceptable standard for measuring adherence. Various ART adherence measures have been used in routine clinical care and research studies. For instance, traditionally, the **self-report**, which relies on patients' recall and honesty, is routinely used, especially in low-income settings, because it is easy to administer and cost-effective. It also can capture a wide range of adherence time windows simply by asking ALHIV about their ART adherence during different intervals of time, within the limits of their recall. However, self-reporting is subject to several biases—such as recall and social desirability biases, and often overestimated adherence (Nance et al., 2017; Orrell et al., 2017). Other measures such as **clinic records** and **pill counts**, have also been used. However, these too have limitations. For instance,

the pill count measure overestimates adherence (Orrell et al., 2017). **Electronic monitoring** using electronic monitoring devices (EMD), despite being more objective, also faces limitations such as their cost and tendency to underestimate adherence (Castillo-Mancilla & Haberer, 2018; Craker et al., 2019).

These shortcomings emphasize the importance of further exploring and refining adherence measurement techniques. Moreover, much of the research on ART adherence measures is from studies conducted among adults. For instance, although the three-item self-reported adherence measure—developed by Wilson and colleagues— has been widely used to measure adherence among ALHIV, it was validated among African-American and Hispanic adults with a mean age of 46 years (Wilson et al., 2016). This leaves a significant gap in our understanding of the performance of adherence methods among ALHIV in low-income settings. Clearly, obtaining accurate adherence data is still challenging, especially among ALHIV in SSA. This dissertation aimed to address this critical gap in the literature by comparing the subjective and objective measures of adherence. Findings from this dissertation study provide additional insights into the performance of the different adherence measures among ALHIV in a resource-constrained setting, a population that is often neglected when developing and validating ART adherence measures. The findings may have practical implications, aiding healthcare providers in selecting appropriate adherence measures and ensuring that accurate adherence data informs clinical decision-making, especially in resource-limited settings.

The need for interventions addressing low ART adherence.

Various interventions have been implemented to improve ART adherence among PLHIV. However, these interventions have often overlooked ALHIV—despite their low ART adherence levels and high HIV-related mortality—with many predominantly focused on adults, especially

those in high-income settings. For instance, in a systematic review conducted by Mbuagbaw and colleagues, only six out of the 49 studies were from SSA (Mbuagbaw et al., 2015), despite the region having almost 90% of the adolescent HIV burden (UNAIDS, 2022b). Additionally, only five of these studies were done among participants below 18 years (Mbuagbaw et al., 2015). Moreover, the few interventions implemented among ALHIV in SSA have so far demonstrated limited success, as indicated by the low ART adherence and viral suppression observed in this population.

In the context of low-resource settings, economic instability is a significant factor that compounds poor ART adherence (Twekambe et al., 2023). For instance, with limited financial resources, ALHIV will struggle to find the money for transportation to attend their medical appointments or meet healthcare-associated costs. To further illustrate, Enane and colleagues conducted a qualitative study on barriers and facilitators of retention in HIV care among adolescents in Kenya and found that the participants highlighted poverty as a major reason for poor engagement in care and adherence to treatment. In the same study, the participants also demonstrated a desire for financial interventions. An excerpt from one of the participants read *"[With a financial intervention], I would just start my business. Because with the job I do sometimes I am not given time to come to the clinic, and you don't feel like leaving it, and there are only two options, you leave the clinic or leave the job.*"(Enane et al., 2020).

Few address poverty despite its central role in undermining treatment outcomes among ALHIV. For example, a systematic review by Damulak et al. found that none of the 31 studies reporting intervention to improve ART adherence in SSA addressed poverty (Damulak et al., 2021). The interventions Damulak and colleagues identified were grouped into five categories, including affective, behavioral, biological, cognitive, and structural interventions. From my

literature search on PubMed, aside from the *Suubi+Adherence* study from which this dissertation derives, no previous RCT has addressed poverty at the household level (Casale et al., 2019; Munyayi et al., 2022).

By boosting household economic stability, EE interventions can address poverty and potentially improve ART adherence. Indeed, findings from the *Suubi+Adherence* have shown a positive impact of EE interventions on ART adherence and viral suppression among ALHIV in Uganda (Bermudez et al., 2018; Brathwaite et al., 2022; Ssewamala et al., 2020). Also, a systematic review of 13 articles found a positive effect of economic interventions on viral suppression among ALHIV. The same systematic review called for further examination and optimization of the EE interventions (Bosma et al., 2023). A significant knowledge gap is that the specific pathways through which the EE interventions exert their influence on adherence remains to be fully explored. Yet, a deeper understanding of these pathways could provide valuable insights into their successful implementation and scale-up in low-resource settings and uncover potential targets for future interventions.

More emphasis on ALHIV at high risk of poor treatment outcomes

In SSA, where healthcare resources are often sparse, there is a dire need to allocate them equitably. In such instances, it is essential to ensure that the ALHIV who require the most support receive it. However, this approach demands an effective strategy to identify and prioritize ALHIV based on their risk profile, ensuring that those most vulnerable to adverse outcomes, like virological failure, receive timely and appropriate interventions. Usually, a poor outcome (such as virologic failure) occurs in a relatively small proportion of the population at risk with the majority successfully achieving viral suppression. The few participants with virologic failure carry a more significant clinical and public health importance since they are at

an elevated risk of spreading HIV and have poor outcomes such as developing opportunistic infections and death. In low-resourced settings, it is not feasible or cost-effective to apply an intervention to the entire population of ALHIV, for purposes of targeting those likely to experience virologic failure.

Predictive modeling has emerged as a powerful machine learning tool in patient-centered care, capable of stratifying ALHIV based on their risk of virological failure and enables providers to tailor interventions and care accordingly. Such a model not only enables clinicians to identify high-risk individuals but also provides insights into the key drivers of virological failure. While the field of risk prediction modeling is relatively new, it holds much promise. Early efforts, like those by Brathwaite et al., have shown the potential of risk prediction models in enhancing HIV care by predicting outcomes such as ART adherence outcomes (Brathwaite et al., 2021). Developing a reliable prediction model for virologic failure contributes to precision medicine in HIV management, emphasizing the need for personalized care strategies based on individual risk profiles.

Aims, Research Questions, and Hypotheses

Aim 1: Compare the performance of self-report, pill counts, and electronic adherence monitoring device (EMD) using Wisepill device in measuring ART Adherence and predicting viral suppression among ALHIV in Uganda.

Research Questions:

1. How reliable is the self-report method compared with pill counts in measuring ART adherence among ALHIV in Uganda?

2. How reliable is the self-report method compared with EMD in measuring ART adherence among ALHIV in Uganda?
3. How reliable is the pill count method compared with EMD in measuring ART adherence among ALHIV in Uganda?
4. Which ART adherence measurement method—self-report, pill counts, or EMD—most accurately predicts viral suppression among ALHIV in Uganda?

Hypothesis: Given the strengths and weaknesses of each adherence measure (Gaifer & Boulassel, 2019; Orrell et al., 2017), the hypotheses tested by this aim are: **H1a.)** Compared to self-reports and EMD, pill counting will be superior in measuring ART adherence and predicting viral suppression among ALHIV. **H1b.)** Compared to self-reports and pill counts, EMD will be superior as a method for measuring ART adherence and predicting viral suppression among ALHIV. **H1c.)** Compared to pill counting and EMD, the self-report is superior as a method for measuring ART adherence and predicting viral suppression among ALHIV.

Aim 2: Develop and validate a model to predict the risk of virologic failure among ALHIV in Uganda.

Research Questions:

1. What is the accuracy (calibration and discrimination) of a model—comprising ***individual*** (age, sex, orphanhood, being in school, depressive symptoms, hopelessness, self-concept, quality of life, HIV knowledge, duration on ART, number of ART drugs, and ART adherence), ***interpersonal*** (household size, and social support, treatment buddy), ***community***

(distance to the hospital, HIV stigma and disclosure) and ***structural*** factors (household assets, food security) — in predicting virological failure among ALHIV in Uganda?

2. What is the influence of the selected individual, intrapersonal, community-level, and structural/institutional levels factors on the risk of virological failure in the model?

Main Hypothesis: Guided by theories including the Health Belief Model, asset theory, and socioecological model, with evidence from a previous risk prediction model for ART adherence among ALHIV (Brathwaite et al., 2021), this aim sought to test the hypothesis that a model—incorporating ***individual*** (age, sex, orphanhood, being in school, depressive symptoms, hopelessness, self-concept, quality of life, HIV knowledge, duration on ART, number of ART drugs, and ART adherence), ***interpersonal*** (household size, and social support, treatment buddy), ***community*** (distance to the hospital, HIV stigma and disclosure) and ***structural*** factors (household assets, food security) —would predict the risk of virological failure among ALHIV in Uganda, with an area under the curve (AUC) of at least 0.8.

Aim 3: Examine the mediators of the effect of an economic empowerment intervention on ART adherence among ALHIV in Uganda.

Research Question:

1. To what extent do factors including *adolescent social transition*, *barriers to medical care,* and *adherence self-efficacy* mediate the relationship between an EE intervention and ART adherence among ALHIV?

Hypotheses: Guided by the Asset theory, **aim 3** tested the following hypotheses: **H3a.)** The EE intervention will have a significant positive effect on ART adherence among ALHIV in Uganda. Participants in the EE intervention group would have higher mean levels of ART adherence

compared to participants in the control group. **H3b.)** There will be an indirect relationship between the EE intervention and ART adherence through the mediating effect of **(1)** adolescent social transition, **(2)** barriers to medical care, and **(3)** adherence self-efficacy. Specifically, participants in the intervention group would have better social transition from adolescents to young adults, report fewer barriers to medical care, and have higher adherence self-efficacy, leading to higher mean ART adherence.

Innovations and strengths of the dissertation

This dissertation is innovative in several ways. ***First***, a key innovation lies in the focus on ALHIV more so in low-resourced communities. While a significant amount of adherence research (and interventions) has often centered on adults (Allison et al., 2022; Nyoni et al., 2020), understanding the unique challenges faced by adolescents during this critical developmental period is crucial for targeted healthcare for this vulnerable population. Thus, a focus on adolescents—a highly non-adherent group (Kim et al., 2017; Kim et al., 2014; Meloni et al., 2020)—is critical, especially as they transition into young adulthood, a very challenging period—both socially and psychologically. This period is marked by a gradual reduction in their dependency on family members (Patton et al., 2016). Consequently, overlooking the needs of the ALHIV presents a pressing public health challenge, especially as we work towards achieving the UNAIDS 95-95-95 targets (UNAIDS, 2014).

Secondly, this dissertation focuses on a comparison of adherence measures among ALHIV. To date, few studies have directly compared the performance of various adherence measures among ALHIV in low-income settings. Unfortunately, most of the existing studies have been constrained by small sample sizes. Moreover, unlike this proposed study, an oversight of many of the previous studies is the lack of emphasis on how the different adherence measures

predict virological failure. Study **Aim 1** addressed these gaps by using a large sample of ALHIV to conduct a comparative analysis of three adherence measures—self-report, pill counts, and the highly objective electronic measure using Wisepill devices.

Another innovation of this dissertation lies in the development of a risk prediction model, making it one of the first studies in SSA to develop a risk prediction model for virologic failure in ALHIV. A comprehensive literature search in PubMed (using different algorithms of the search terms "HIV," "viral suppression," "risk prediction," "adolescents," and "Sub-Saharan Africa") yielded no prior studies that have developed prediction models for viral failure among ALHIV in SSA. The only risk prediction model among ALHIV in SSA was developed by Brathwaite, where she used psychosocial and economic factors to predict ART adherence. Overall, this risk prediction model holds the promise of identifying ALHIV more likely to experience virologic failure. By predicting this group promptly, targeted, and timely interventions can be implemented to prevent virological failure and guide appropriate healthcare resource allocation.

Lastly, to my knowledge, no study has previous assessed adolescent transition and barriers to medical care as mediators between EE interventions and ART adherence. This gap is rather surprising, given the vulnerabilities that adolescents face during their transition to adulthood (Patton et al., 2016). Moreover, this aim was achieved by employing robust methodological approaches including a cluster-randomized controlled study design and Structural Equation Modeling *(*SEM). The SEM enables the simultaneous investigation of multiple paths within a single model. In addition, by conducting a longitudinal mediation analysis, this study accounted for temporal effects, capturing changes in mediating processes over time.

Chapter 2: Literature Review

Burden of HIV/AIDS

Global burden of HIV

Globally, over 38.4 million people are living with HIV, of whom six million do not know their HIV status (UNICEF, July 2021). Almost 70% of PLHIV are in sub-Saharan Africa (SSA), an indication of how HIV/AIDS disproportionately affects Africa—since Africa contributes only 12% of the world's population (UNAIDS, 2021b). In 2021, 1.5 million people became infected with HIV globally— representing a 32% decline in HIV infection since 2010, when 2.2 million people became infected (UNAIDS, 2022a). Despite the declining incidence of HIV, new infections are still high. Unless the trends are reversed, another 1.2 million people will become infected with HIV by 2025.

The burden of HIV among adolescents in SSA

Of the 1.8 million ALHIV, 89% (1.5 million) reside in SSA (UNAIDS, 2021b). Eastern and Southern African regions carry the highest burden of adolescent HIV, contributing a combined 1.2 million ALHIV, representing 70% of all ALHIV globally. Meanwhile, another 330,000 ALHIV (19%) reside in Central and West Africa. Sub-Saharan Africa faces gender disparities in the incidence and prevalence of adolescent HIV. However, it is worth noting that the high prevalence of HIV among adolescents is partly attributed to the increased survival of perinatally infected children following the discovery and access to ART (Munthali et al., 2020; Slogrove et al., 2018).

On a positive note, UNICEF data showed that the incidence of HIV in adolescents in the Eastern and Southern Africa region has reduced by 41% since 2010, making it one of the most

rapidly declining HIV rates in this population globally (UNICEF, 2021). Unfortunately, this rate of decline is not fast enough to meet the 2030 global targets. Moreover, the HIV-related mortality rate has remained high in adolescents in this region. While some progress has been made in reducing the incidence of adolescent HIV in SSA, much more needs to be done to improve outcomes such as improving adherence and viral suppression and reducing the mortality rate in this region to meet the global targets. Therefore, this area statement mainly focuses on ALHIV in SSA.

Consequences of HIV

HIV directly and indirectly results in **psychological** conditions such as stigma and depression, which impact the mental health functioning of the ALHIV. Unfortunately, such conditions affect how well the adolescents adhere to ART and cope with the illness and have significant implications on the survival of ALHIV.

Socially, HIV has disrupted family structures by causing the death of many parents, thus rendering many children orphans (Leyenaar, 2005). Globally, almost 15 million children and adolescents (0 - 17 years) have been orphaned by an HIV-related cause (USAID, 2016), representing 10% of all adolescent orphans. Orphanhood due to HIV has affected SSA the most, with three-quarters (11 million) of the HIV-related orphans residing in SSA (WHO, 2021). Consequently, many households are led by children and adolescents, while in other homes, grandparents have taken over the parent roles, where children live in extended families (Hosegood et al., 2007).

HIV has a synergistically devastating relationship with **poverty**, whereby HIV leads to financial constraints in the affected families (MacCarthy et al., 2018). On the other hand, poverty leads to HIV spread and poor treatment outcomes among ALHIV (Ridgeway et al., 2021). The

HIV-poverty relationship is more apparent in SSA—a region much affected by poverty and the burden of HIV is higher than that in high-income settings (Pascoe et al., 2015; Ridgeway et al., 2021).

Antiretroviral Therapy

Definition and benefits of antiretroviral therapy

This dissertation adopted the WHO definition of ***antiretroviral therapy***—as the drugs used to treat HIV infection (WHO, 2016). Effective treatment against HIV, ART, was discovered five years after the HIV was identified. There are over 21 FDA-approved antiretroviral agents (Martinez-Cajas & Wainberg, 2008). Selection of the best regimens depends on many factors including side effects and toxicity profiles, comorbidities such as liver and kidney problems, food restrictions, and drug-drug interactions (Piacenti, 2006). ART regimens are combined to achieve maximal efficacy while minimizing treatment-related adverse effects, delaying the development of viral resistance, preserving drug options, and ensuring maximal adherence.

Adherence has been defined as the extent to which a patient's behavior corresponds with the prescribed medication dosing regime, including time, dosing, and interval of medication intake (Morrison et al., 2015). Besides reducing mortality and prolonging survival, ART has additional benefits, such as reducing comorbidities and improving the quality of life in the PLHIV (Slogrove et al., 2018). At the population level, ART has been critical in reducing the vertical transmission of HIV from the mother to the unborn baby (Hurst et al., 2015; Paintsil & Andiman, 2009).

ART coverage and adherence among ALHIV

ART has improved survival in the PLHIV (Munthali et al., 2020). Currently, ART is widely available, with 75% of PLHIV having access to ART in 2021 (UNAIDS). Overall, 28.7 million people are on ART (UNAIDS, 2022a), compared to only 7.8 million in 2010. However, to date, there is no cure for HIV, with ART only being able to suppress HIV and improve survival and quality of life (Meloni et al., 2020). Adherence continues to be a significant challenge, especially among ALHIV.

Less than two-thirds of ALHIV, 59%, are receiving ART, which means that more than 700,000 ALHIV are not receiving life-saving ART (UNAIDS, 2021b). Notably, the number of adolescents receiving ART has increased steadily from 200,000 in 2010 to 1 million ALHIV in 2021 (UNAIDS, 2021b). Despite the increased ART coverage among ALHIV, adherence remains significantly low. To illustrate, a systematic review of ART adherence among ALHIV have revealed alarmingly low levels of adherence, with some studies reporting rates as low as 6% in certain settings (Ammon et al., 2018). These findings imply that efforts to ensure improved ART adherence among ALHIV must be ramped up if the 95-95-95 targets (95% of all PLHIV to know their status, 95% of those diagnosed to be on ART, and 95% of those on ART to achieve viral suppression) are to be realized by 2025 (Frescura et al., 2022).

Enablers and barriers to treatment adherence among ALHIV.

The factors that hinder or facilitate ALHIV adherence to HIV treatment (hence influence viral suppression) can be grouped according to the different levels at which they exert their influence, including the individual, interpersonal, community, institutional, and policy levels as classified by the *socioecological model* (discussed in chapter three).

Individual level.

Individual factors affecting treatment adherence among ALHIV include age, sex, education level, attendance at school, and substance use (Sileo et al., 2019). Available data shows that older adolescents have poorer adherence than younger adolescents (10-14) (Ammon et al., 2018; UNICEF, 2022). Sex is another individual-level factor influencing ART adherence among ALHIV. Data from LMICs, especially in SSA, has shown that females have better treatment adherence than males (Adejumo et al., 2015; UNICEF, 2022). Adolescents with low education levels and those not in school have poorer ART adherence than those in school (Denison et al., 2018; Kose et al., 2021). Alcohol and drug abuse were also associated with poor adherence (Denison et al., 2018).

Furthermore, literature has consistently shown that **depression**, common among ALHIV, is a strong predictor of ART adherence (Kim et al., 2017; Smith Fawzi et al., 2016). Several mechanisms, such as hopelessness and loss of orientation towards future aspirations, have been suggested as possible explanations for the inverse relationship between depression and ART adherence (Smith Fawzi et al., 2016).

Treatment-related factors, including drug side effects like severe diarrhea, body dysmorphia (altered body shape such as the development of a hump – associated with stavudine), vivid dreams (more marked with efavirenz), and liver, kidney, and nerve damage, discourage the patients from taking their medicine as prescribed (Adejumo et al., 2015; Ammon et al., 2018). Other factors, such as treatment duration, the number of pills — also known as the pill burden— that the patient takes and the frequency of taking medication daily, also affect adherence (Ammon et al., 2018).

Other individual level factors that impact ART adherence include the lack of knowledge about HIV/AIDS, perceived stigma, and forgetfulness—which hinder ART adherence, and self-motivation (Ankrah, 1993; Groh et al., 2011; Shubber et al., 2016).

interpersonal level

Social factors such as social support and family cohesion, improve adherence to ART (Adejumo et al., 2015). Various explanations exist for the positive effect of **social support** on ART adherence. For instance, support from a treatment supporter enables the ALHIV to adhere to their medication since the treatment supporters remind the adolescent to take their medication. In addition, the treatment supporters ensure that the ALHIV attends hospital appointments to have medication refills and routine reviews from the doctors. In our recent article, we demonstrated the positive role of family support in improving ART adherence among ALHIV through the mediating effect of communication with the caregiver (Proscovia Nabunya et al., 2023). Unfortunately, many ALHIV come from families that HIV has disrupted and may lack the social and family support from parents, which hampers treatment adherence.

Adolescent social transition: During their transition from childhood to adulthood, adolescents assume increasing responsibility, which for ALHIV will include added responsibility for treatment adherence (Patton et al., 2016). *Social transition*—defined as the process of adapting to changing social relationships as they move from adolescence to adulthood— is in various forms including money and work, residential independence, and healthcare transition readiness (Scales et al., 2016). As ALHIV approach adulthood, they must transition from pediatric to adult-focused health care systems. ALHIV may have relied on parents and guardians to help manage their healthcare needs. The transition to adult-focused care represents a significant shift, as ALHIV must develop self-care management skills, such as taking their

medication on time, knowing when to attend medical appointments, and communicating effectively with healthcare providers. The loss of treatment support can interrupt adherence. Moreover, in the transition stage, adolescents form romantic relationships, which may deter disclosure and ART adherence, and increase the risk for HIV transmission.

In addition, early adulthood marks a period when one is ready to start formal employment. ALHIV often face unique challenges when seeking employment opportunities (Keller et al., 2007). Due to possible stigma and discrimination, they may be more likely to experience unemployment or have limited access to formal employment (Sprague et al., 2011). As a result, this can limit their financial independence and pose additional challenges in terms of accessing resources for their HIV treatment. Furthermore, ALHIV may miss work due to HIV-related illnesses or the need to attend medical appointments, which can affect their ability to maintain employment (McGoldrick, 2012). Besides the challenges of seeking and maintaining work, ALHIV also undergo a transition related to residential Independence. To illustrate, many ALHIV live with their families, but as they grow up, they may want to live independently and start their own families. When ALHIV transition out of their family homes, they may lose social support and family support, which can impact their ability to manage their health and well-being.

Community level

Disclosure has consistently stood out as a major barrier to ART adherence (Shubber et al., 2016). To illustrate, ALHIV who have not disclosed their HIV status to the member in the communities where they live may be forced to skip medicine for fear of disclosing their HIV status (Adejumo et al., 2015). Other psychological factors impacting adherence include **enacted stigma and discrimination**. ALHIV may face stigma from hospital personnel— i.e., enacted stigma— or the fear or expectation of being stigmatized— i.e., anticipated stigma (Ahmed et al.,

2017). Either way, stigma negatively impacts treatment adherence and limits ALHIV from attending hospital appointments.

Multiple studies have emphasized the importance of **access to care** in determining adherence to the ART (Kagee et al., 2011; Reda & Biadgilign, 2012). Access to care is multi-dimensional, encompassing elements such as the availability of healthcare facilities, geographic proximity, affordability, and acceptability of care. For ALHIV in low-resource settings, barriers to healthcare access often include poverty, long distances to clinics, lack of youth-friendly services, and stigma associated with HIV, among others. These barriers can interrupt the continuity of ART, leading to suboptimal medication adherence, increased viral load, and elevated risk of developing drug resistance.

Structural and policy levels.

Household poverty: Literature has consistently shown that financial challenges hinder adherence to the ART (Ahmed et al., 2017; McAllister et al., 2013). For instance, poverty contributes to food insecurity creating challenges for ALHIV in maintaining proper nutrition; yet many ART regimens require the patient to take medicine after a meal. When ART is taken on an empty stomach, its pharmacokinetics (such as absorption and distribution) are affected, which lowers its efficacy (Kagaayi & Serwadda, 2016; Kimera et al., 2020). Through this and other mechanisms, **food insecurity** affects adherence. In addition, ALHIV and their families often struggle to afford the costs associated with medication, and transportation to healthcare facilities. Consequently, ALHIV may experience irregular medication usage, treatment interruptions, or even complete non-adherence.

At an institutional level, **healthcare systems** must offer comprehensive, youth-friendly services tailored to the unique needs of ALHIV (Shubber et al., 2016). This encompasses

specialized healthcare providers, adherence counseling, regular follow-up, consistent medication supply, and maintaining confidentiality, privacy, and respect. Simultaneously, robust **health policies** are crucial at the policy level. These policies should advocate for free or subsidized access to ART, promote HIV education at health facilities (but also in schools), as well as enact firm policies against HIV stigma. Policymakers have the power to allocate adequate **funding and resources** for healthcare institutions are also necessary to overcome systemic barriers to ART adherence.

Measures of Adherence to Antiretroviral Therapy

Throughout the LMICs, researchers acknowledge that it is challenging to accurately determine ART adherence (Berg & Arnsten, 2006). Although many measures have been developed to monitor ART adherence, none is accepted as the gold-standard test since they all have significant limitations (Castillo-Mancilla & Haberer, 2018). Below is a discussion of the strengths and limitations of the common adherence measures.

Self-report is one of the most common measures of ART adherence, largely due to its affordability and practicality compared to other measures. This method generally involves the patient reporting on their own medication-taking behaviors, either through interviews or questionnaires (Orrell et al., 2017). It allows for quick and straightforward data collection, making it particularly suitable for routine clinical practice. However, self-reports have been criticized for being prone to recall bias (Zhou et al., 2021). Moreover, ALHIV may not solely responsible for managing their medication; often, caregivers share this responsibility. Thus, self-report measures that do not account for caregiver input may provide an incomplete and potentially inaccurate representation of the adolescent's adherence behaviors (Hodes et al., 2020).

Routinely, ALHIV visit the hospital for HIV care and **medical refills**—which can be used to measure adherence. The method involves a retrospective review of patient pharmacy records to determine the number of surplus pills the patient returns with, which are then used to calculate adherence. The pharmacy refill measure of ART adherence is relatively cheap and can be used in routine clinical care and research, including in low-income settings. Also, the method does not depend on the patient's memory; hence it is free of recall and social desirability biases. However, pharmacy refill is affected by missing data on pills dispensed, especially in LMICs, where data storage is usually paper based. Also, the patient can manipulate the number of balance pills when returning for pharmacy refills, which overestimates adherence (Grossberg & Gross, 2007). *Finally*, ART adherence based on pharmacy refills does not account for pill sharing in situations where the patient either gives away or receives pills.

Pill count involves counting the number of pills left in a patient's possession and comparing this to the number that should remain according to the prescribed regimen. This method provides an objective and cost-effective measure of adherence, is inexpensive, easy to implement, and free of recall bias; hence it is commonly used in low-income settings in SSA. However, pill counts require consistent and accurate counting and record-keeping by healthcare providers or caregivers, which may be challenging in resource-constrained settings. Furthermore, the pill count method can be influenced by pill-sharing behaviors, where patients may share their medication with others, which usually goes unnoticed. Another shortcoming of pill counts is that the patients can manipulate the measure by discarding some pills— also called “pill dumping.” Both pill dumping and pill sharing lead to an overestimation of actual adherence. (Biressaw et al., 2013). Finally, like self-reports, pill counts may not capture the full complexity of adherence

behavior. They do not provide information on the timing of doses, or the context surrounding missed doses.

Electronic adherence monitoring (EMD) involves using an electronic monitoring device (EMD) such as the Wisepill device—used in this dissertation—which stores the participant's pills (Haberer et al., 2010). These devices record each instance a medication container is opened, providing detailed data about the real-time medication-taking patterns over time. EMD circumvents many of the issues associated with self-reporting, such as recall and social desirability bias, and offers a more granular level of data than pill counts. Moreover, EMD has an added advantage in that it measures adherence in real-time, which provides an opportunity to intervene early enough if the patient is not adhering well to the medication. In addition, the method is free of recall bias since it does not rely on the participant's memory (Haberer et al., 2010).

However, despite the potential advantages of EMD, its applicability, particularly among ALHIV in resource-limited settings, faces significant challenges. The primary challenge is cost. EMDs are typically more expensive than traditional adherence measurement methods. This economic burden can pose a substantial barrier in low-resource contexts, potentially limiting the feasibility and scalability of EMD. Additionally, EMD often requires reliable telecommunications network connectivity for data transmission, a prerequisite that may not be consistently available in all areas, particularly in some parts of Sub-Saharan Africa. Network instability can lead to data loss or incomplete data, compromising the accuracy and reliability of adherence measurements. Moreover, while EMD provides objective data on pill bottle or box openings, it does not guarantee that the medication was ingested, leaving room for potential discrepancies between recorded and actual medication intake.

Viral load monitoring is among the most reliable indicators for response to ART. In Uganda, the national HIV care guidelines recommend viral load testing at least once every six months (Health, 2020). However, for various reasons such as the cost implications, viral load testing is not always done. Besides the cost limitations, additional factors such as the need specialized laboratory equipment and specially trained personnel, which are not readily available in many hospitals in LMICs further limit the use of viral load testing in ALHIV in resource-constrained settings. Moreover, the VL testing takes several days to return patient results, which also limits the use of VL in routine practice.

As a result, clinicians often rely on monitoring adherence as a proxy for achieving viral suppression. However, it is worth noting that ART adherence is not always an accurate indicator of viral suppression. For instance, it is also possible for individuals to maintain good ART adherence yet not achieve viral suppression, especially if they are dealing with drug-resistant viral strains. On the other hand, in recent years, there have been tremendous advances in ART, such that even with adherence as low as 85%, patients can achieve viral suppression. Hence, some ALHIV with low adherence can achieve viral suppression (Gordon et al., 2015). Therefore, viral load measurement also has limitations.

In summary, ALHIV represent a particularly vulnerable group in the fight against HIV/AIDS, especially in SSA, which bears a significant burden of the disease. Various enablers, such as social support play a pivotal role in promoting adherence. On the other hand, barriers like fear of disclosure hinder optimal adherence levels. Accurate measurement of adherence is also still a challenge, with various measures being used yet each faces significant limitations.

Chapter 3: Theoretical and Conceptual Frameworks

Theories provide a critical link between social and behavioral sciences and biomedical research. For instance, when biomedical research found that ART was effective in suppressing HIV and improving survival and quality of life in PLHIV (Ford et al., 2011; Kagaayi & Serwadda, 2016), it was assumed that all PLHIV would eagerly take ART. However, over three decades since ART was discovered, sub-optimal adherence is still observed among populations such as ALHIV (Vella et al., 2012). Therefore, the need for employing theories to understand ART adherence cannot be emphasized enough.

Several theoretical frameworks and models could be applied to inform poor adherence. These can be grouped into those that are: (1) theories focused on the individual, for example the **Health Belief Model (HBM)** (Champion & Skinner, 2008; Hochbaum et al., 1952), and the **Asset Theory** (Sherraden, 1990); and (2) those that are structurally focused—looking at institutions and structures that may impact individual adherence, represented here by the **Socio-ecological model** (Kilanowski, 2017). Thus, the dissertation proposal recognizes this complementarity and applies the three complementary theories as detailed below.

The Health Belief Model

A group of U.S. social psychologists, including Rosenstock, Hochbaum, Kegeles, and Leventhal, developed the Health Belief Model (HBM) in the 1950s (Hochbaum et al., 1952; Houchbaum, 1958). The model was developed as a conceptual framework to understand how health-related behaviors can be changed or sustained (Champion & Skinner, 2008). The HBM has been used in various contexts, including understanding medication adherence (Becker, 1974; Kip et al., 2009). Kips et al., 2009, applied the theory to understand divers of poor ART adherence in an adult cohort of PLHIV in Botswana (Kip et al., 2009). This dissertation

conceptualizes ART adherence as a health behavior that needs to be enhanced and uses the HBM to examine the key areas that could be targeted to model ART adherence to improve secondary outcomes like viral suppression.

The HBM was crucial in guiding the selection of the independent factors to include in the risk prediction model for virologic failure **(Aim 2)** and to inform the conceptualization of **Aim 3** (which examines the mediators of the effect of an EE intervention on ART adherence). The discussion below expounds on the HBM and how it guided the conceptualization of this dissertation.

Constructs of the HBM

HBM asserts that individuals will only change their behaviors if certain conditions are met; including **susceptibility** to the consequences of undesirable behavior, the **severity** of the behavior and its consequences when the **benefits** of changing the behavior outweigh the barriers, the presence of **cues to take action**, and whether the individuals have the **self-efficacy** to undertake the necessary behavior or behavioral change (Champion & Skinner, 2008; Hochbaum et al., 1952; Houchbaum, 1958). See **Figure 1** below.

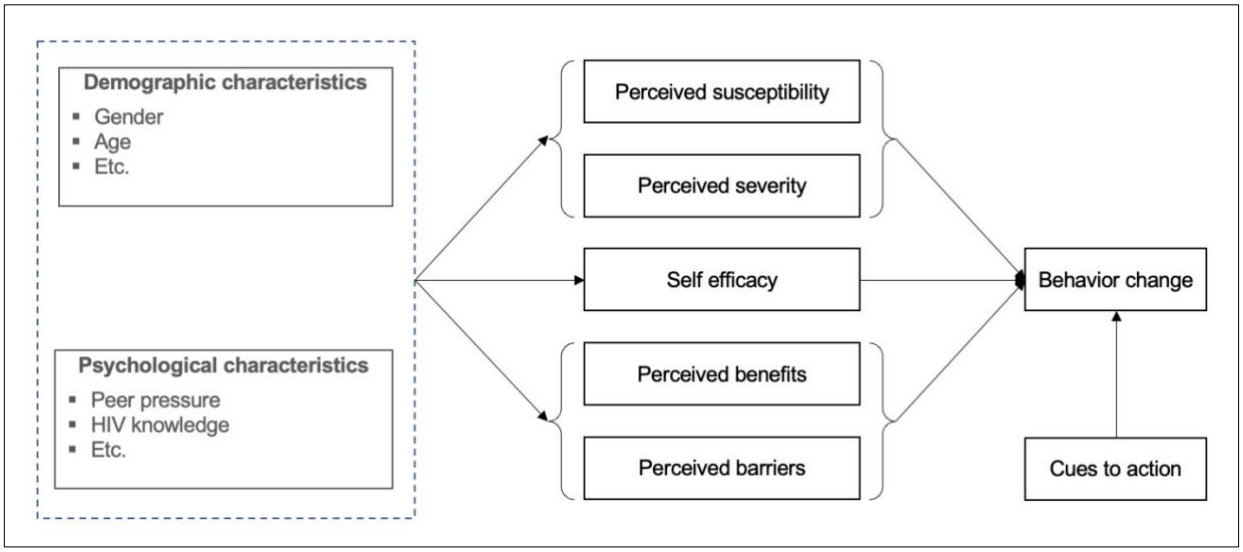

Figure 1: The Health Belief Model

Perceived susceptibility. Individuals will develop the need to change their behavior when they feel susceptible to the consequences of an undesirable behavior. *Perceived susceptibility* is an individual's subjective perception of the likelihood of acquiring a condition (Champion & Skinner, 2008). Applying the HBM to ART adherence, ALHIV need to feel susceptible to the consequences of poor adherence (such as disease progression and death) as one of the conditions for improving their adherence. Kip et al., 2009, used the HBM and demonstrated that susceptibility was a significant contributing factor to ART adherence in a young adult HIV sample in Botswana. In their study, some participants, over 40% of the 400 participants, believed they could not get reinfected with HIV and did not see the need to adhere to ART (Kip et al., 2009). It is not surprising that ART adherence among this group was low.

Perceived severity. The HBM posits that unless the individual perceives the undesirable behavior, or its consequences, as being severe enough, they will not feel the need to change the behavior (Champion & Skinner, 2008). In line with the HBM, this dissertation conceptualizes the perceived severity of the undesirable behavior – poor ART adherence— as virologic failure. Viral non-suppression is followed by the rapid progression of HIV to AIDS, the development of opportunistic infections, and higher chances of mortality, among other consequences (Meloni et al., 2020). In Kip's study in Botswana, discussed above, 48% of the participants did not consider HIV to be a severe disease, while 30% believed that HIV was curable (Kip et al., 2009). In the HBM, the perceived susceptibility and severity are combined into *the threat*. In this dissertation, HIV knowledge (which was measured on a scale with some items assessing susceptibility to poor treatment outcomes and others assessing the perception of the severity of HIV/AIDS) was included as one of the independent factors in developing the risk prediction model for virologic

failure (**Aim 2**). We hypothesize that those with low knowledge of HIV/AIDS will be more likely to assess themselves as being less susceptible to HIV and will assess the disease as being less severe; hence will be less likely to adhere to ART, consequently having low viral suppression.

Perceived benefits. Before changing their behavior, individuals evaluate the benefits that come along with it and will only consider changing their behaviors when they foresee some benefits (Hochbaum et al., 1952). Tailoring this construct (health benefits) of the HBM to this dissertation, the behavior being modeled is ART adherence, and the perceived benefit of improving this behavior is viral suppression—the outcome for the **second aim** of this dissertation (developing and validating a risk prediction model). With viral suppression, there are associated secondary benefits, such as prolonged survival, and improved quality of life (Meloni et al., 2020)—which were not assessed in this dissertation. ALHIV may also evaluate the benefits of adherence in the form of social outcomes, such as reducing the chances of missing school or playing with peers due to illness (Guo et al., 2012; Kimera et al., 2019; Pufall et al., 2014). The benefits may also be perceived economically, such as saving money by reducing hospital admissions or work time lost while admitted (Pascoe et al., 2015).

Perceived barriers play a crucial role in determining whether a desired change in behavior will occur. According to the HBM, it is not enough for individuals to simply acknowledge these conditions; they must also confront and overcome the perceived barriers that hinder them from making positive changes in their health behavior. In the context of the HBM, barriers refer to the obstacles that individuals perceive when considering taking action to improve their health behavior (Champion & Skinner, 2008). For ALHIV, the barriers may include factors such as poverty, whereby ALHIV may not have money for transportation to the

hospital for medical appointments, and poor access to hospitals, among other factors. A qualitative study of ALHIV in Uganda grouped the barriers to ART adherence into four themes including poverty, school attendance, family support, and the burden of taking multiple pills (MacCarthy et al., 2018).

Against this background for **Aim 2**, which develops a risk prediction model for virologic failure, several factors were included in the model after being conceptualized as barriers to ART adherence and viral suppression according to the HBM and backed by empirical evidence (Brathwaite et al., 2021; Damulira et al., 2019; Okawa et al., 2018). These factors include asset ownership (a proxy for poverty), social support, mental health, HIV stigma, and pill burden in the form of number of pills taken per day and the number of times that the ALHIV takes ART per day. Furthermore, (and drawing from the Asset theory), barriers to medical care were selected as one of the mediators in **Aim 3**— which assessed the mediators of the impact of an intervention on ART adherence. We hypothesized that by addressing barriers to medical care, the intervention would have an indirect effect in improving ART adherence.

Cues to Action. The HBM emphasizes that the presence of the constructs mentioned earlier may not be sufficient to result in a behavioral change, but instead, specific cues must trigger the behavioral change (Becker, 1974; Champion & Skinner, 2008). These cues act as reminders that prompt individuals to act toward changing their behavior. In the context of adherence to ART, cues play a crucial role in prompting and motivating individuals to improve their adherence. They take various forms and may include factors such as counseling from healthcare workers regarding the importance of adherence, reminders about medication schedules, or noticeable biological deteriorations due to poor adherence, such as worsening symptoms or a decline in overall health. For this dissertation, having acknowledged the

deterioration in health as one of the cues to action, self-reported quality of life, was included as one of the predictors in developing the risk prediction model for virologic failure **(Aim 2).**

Self-efficacy. Bandura defined *self-efficacy* as "the conviction that one can successfully execute the behavior required to produce outcomes" (Pajares, 1997). Applying the HBM to ART adherence, self-efficacy refers to an individual's belief in their own ability to take ART as prescribed, to realize the benefits of ART such as viral suppression, and prolonged survival. The HBM suggests that individuals with higher levels of self-efficacy are more likely to engage in health-promoting behaviors, as they believe they have the skills and capabilities to overcome any obstacles or challenges that may arise. Available evidence confirms the role of adherence self-efficacy in impacting the ART adherence (Crockett et al., 2020; Johnson et al., 2007). For this reason, in developing the risk prediction model for virologic failure, ART adherence self-efficacy measured using the self-efficacy scale, was included as one of the predictor variables. Similarly, adherence self-efficacy was included as a mediator for the effect of the EE intervention on ART adherence, acknowledging that the intervention, and the two other mediators (including the barriers to medical care and adolescent social transition) exert their influence on ART adherence by enhancing the ALHIV's adherence self-efficacy.

The above HBM constructs are moderated by other variables, such as sociodemographic and psychological characteristics, which will be included in the risk prediction model for virologic failure (**Aim 2**).

The Asset Theory

Michael Sherraden's *theory of welfare based on assets (the Asset Theory)* challenges the conventional approach to poverty alleviation by focusing on assets as the critical measure of

household wealth (Sherraden, 1990). The theory proposes that assets, including financial and physical resources, provide a more comprehensive and sustainable form of welfare than income, which is seen as merely a transitory source of support. This theory emphasizes the importance of asset accumulation for individual and household well-being, positing that owning assets not only fosters financial stability and educational advancement but also bolsters non-economic benefits such as psychological, behavioral, and social assets (Sherraden, 1990; Sherraden & Gilbert, 2016).

In the context of ALHIV, poverty can compound HIV-related challenges and lead to poor adherence. For example, Kalichman and colleagues, (2010) demonstrated that poverty was a significant predictor of poor ART adherence among people with HIV living in low-income settings (Kalichman & Grebler, 2010). Poverty can also affect ART adherence indirectly through impacting factors such as barriers to medical care and adolescent mental health (Azia et al., 2016; Patricia Cavazos-Rehg et al., 2021). These factors can also contribute to poor adherence to medication regimens, which is critical for managing the virus and maintaining good health (MacCarthy et al., 2018). On the other hand, economic, health, and psychological empowerment are multidimensional benefits gained from economic empowerment interventions. The application of the asset theory in Uganda has shown improved health outcomes among adolescents infected with or affected by HIV (Bermudez et al., 2018; Brathwaite et al., 2022; Dvalishvili et al., 2022; Kizito, Nabayinda, Kiyingi, et al., 2023; Ssewamala et al., 2020), but the mechanisms of change are not well studied. Hence, this dissertation draws from the asset theory to 1) include asset ownership as a predictor in the risk prediction model for virologic failure **(Aim 2)**, and 2) select the potential mediators of the effect of an EE intervention on ART

adherence **(Aim 3)**. The theoretical underpinnings—as elaborated in the Asset Theory—through which assets result in health-related benefits are discussed below.

Assets as a source of household financial stability.

Low-income families without sufficient assets are often vulnerable to financial insecurity and poverty when faced with such events. For HIV-affected families, asset ownership can provide a crucial safety net against the negative impact of the disease such as the loss of income through medical costs, lost productivity due to illness, or death of the household head—leaving orphaned children. By accessing resources through their assets, these families can cope with such tragic events. As an example, an article published by Ruth Evans (2012), showed that families led by orphaned children—having lost the head of household—were more resilient to chronic poverty thanks to the asset inheritance (Evans, 2012). Upon this premise, **aim 3** examined *barriers to medical care* as one of the mediators for the impact of the EE intervention on ART adherence. The choice of this mediator was guided by the argument laid by the asset theory that when they accumulate assets, ALHIV and their families will remain stable and have enough resources to cater for the necessary health-related costs, which are critical for ART adherence. Moreover, the direct effect of the EE intervention on outcomes including ART adherence and viral suppression has been demonstrated through our earlier research (Bermudez et al., 2018; Brathwaite et al., 2022).

Assets create an orientation toward the future.

The *asset theory* argues that low-income individuals are focused on immediate survival and basic needs and are less likely to plan for their future. However, with greater asset ownership, individuals and families can access new opportunities and resources, enabling them to envision a more positive future for themselves.

Upon this background, the **third aim** of this dissertation assessed *adolescent social transition* as one of the pathways through which economic empowerment impacts ART adherence. Adolescent transition was defined through three dimensions, namely residential independence, money and work transition, and healthcare transition readiness. The link between asset ownership and successful adolescent transitions stems from the inherent orientation toward the future that asset ownership fosters. For instance, assets can contribute to healthcare transition readiness by providing adolescents with the means to afford necessary medical care and engage in self-care practices. To demonstrate, in a narrative review by Narla et al., (2021) discussing pediatric to adult healthcare transition in resource-limited settings, financial difficulties stood out as one of the major barriers to smooth healthcare transition for these adolescents (Narla et al., 2021).

Assets promote social power.

In the HIV context, ALHIV who have limited resources face the unique challenge of dealing with both HIV and poverty, often leading to negative psychological effects such as low self-concept and feelings of worthlessness. However, research suggests that asset ownership can play a crucial role in mitigating these negative effects (Patricia Cavazos-Rehg et al., 2021). By acquiring and owning assets, ALHIV can address poverty, and hence overcome the negative traits associated with their circumstances. As a result, these adolescents develop a sense of empowerment and belonging, which boosts their self-perception and self-esteem. Thanks to the elevated self-image, these adolescents can form and sustain meaningful social networks and gain more support from their peers. Moreover, existing literature confirms the crucial role of social support in improving ART adherence among ALHIV. For instance, in our recent publication, we found direct and indirect effects of family support in boosting ART adherence in the ALHIV (P.

Nabunya et al., 2023). A study done among 702 ALHIV in Uganda found that social support was significantly associated with improved ART adherence (Damulira et al., 2019). Similar results have been reported in other similar settings (Jimu et al., 2021).

Other benefits of assets.

There are other benefits that assets have on individuals and families that improve their well-being, such as providing a foundation for risk-taking and increasing personal efficacy. These benefits are especially relevant for ALHIV. For example, taking calculated risks enables ALHIV to explore new opportunities and build their future. On the other hand, increased personal efficacy, which may come from having control over financial decisions, can help the ALHIV feel more confident and self-sufficient and, in turn, better manage their health and adhere to their medication. Overall, these benefits of asset ownership are crucial for the long-term stability, success, and well-being of ALHIV and play a significant role in their ability to navigate the challenges associated with living with HIV.

Socioecological model

The social-ecological model examines the interactions between an individual and the environment. It is based on the principle that individuals do not live in a vacuum. Therefore, the individuals and their entire ecological system must be considered to understand human behavior and health outcomes. Individuals and factors beyond the individual interact with one another to influence biological and behavioral outcomes in individuals (Kilanowski, 2017). However, individuals can only manipulate the individual factors and those factors in their immediate environment. The model was first proposed by Urie Bronfenbrenner in 1979 when he published his Ecological Systems Theory of Human Development (Bronfenbrenner, 1979). This theory was

initially developed as a conceptual model and was later developed into a theory in the 1980s (Carlson & Cassel, 1984). In this model, Bronfenbrenner asserted that the ecological system is divided into four ecological systems, including the micro-, miso-, exo-, and macro. In his original theory, Bronfenbrenner posits that these ecological systems interact with each other in influencing individual outcomes.

Levels of the social-ecological model.

Although Bronfenbrenner developed the Ecological Systems Theory to understand the influences of human development, this theory-based framework would later be revised to give rise to the social-ecological model (Carlson & Cassel, 1984).

The model has been adapted to other contexts (Akinyemiju et al., 2022; Jason et al., 2017). When applied to understanding ART adherence, the social-ecological model divides the ecological system into various levels, including the individual, interpersonal or networks, community, structural and institutional, and structural (Kaufman et al., 2014). Also, see **Figure 2**. The socio-ecological model was used to guide the selection of the variables to include in the risk prediction model for this dissertation **(Aim 2).**

The **individual (intrapersonal)** level mainly includes biological and behavioral factors influencing individual health. Guided by the socioecological model, the following variables, at the individual level, were included in the risk prediction model for virologic failure **(Aim 2)**. The participants' age, gender, HIV knowledge (including the knowledge benefits of adherence), ART adherence self-efficacy, and quality of life. Indeed, evidence exists to support the relationship between these factors, ART adherence, and viral suppression (Brathwaite et al., 2021; Kim et al., 2017). The socio-ecological model asserts that the individual level is affected by (and affects) the immediate physical and social environment.

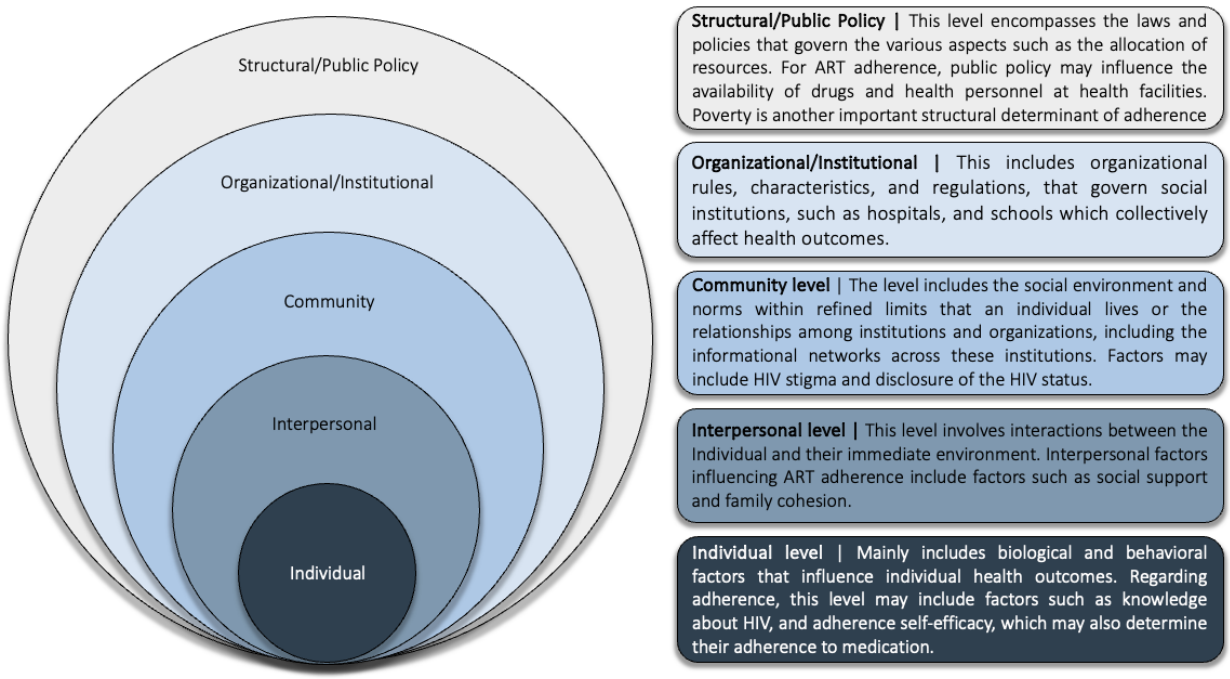

Figure 2: A socioecological model for the factors influencing HIV-related behavior.

The **interpersonal/relationship** level comprises those factors such as social and family support— including friends, neighbors, and other connections— that support the ALHIV to achieve and maintain health-promoting behavior such as adhering to their medication—resulting in suppressed viral load and its benefits. Literature shows that social support, and family cohesion, are critical in determining to what extent ALHIV adhere to their medication (Becker et al., 2020; Scheurer et al., 2012), and impact viral suppression (Brown et al., 2021). Hence, in this dissertation, social support was considered a potential predictor in developing the risk prediction model for virologic failure **(Aim 2)**.

The **community level** deals with the influences at a larger group level—such as the social environment and social norms—that influence health outcomes. This level is more concerned with the broader context in which ALHIV reside. For ALHIV, factors such as HIV stigma and disclosure of HIV status influence the viral suppression (Mugo et al., 2023). Hence, both factors

were included as predictors in developing the model to predict the risk of virologic failure (**Aim 2**).

The **organizational/Institutional** level includes the rules, regulations, guidelines, or policies within institutions and organizations that impact an individual's health and behavior. For instance, although not assessed in this dissertation, health system factors that could affect how well ALHIV adhere to ART include the availability and quality of HIV care services, operational hours of the clinics, competent healthcare teams, drug stockouts, confidentiality/privacy, and the integration of services.

At the **structural level**, policies and laws significantly impact individual health by influencing the levels beneath them. Factors at this level may include the political context and priorities, access to services—including how close the clinics are to the ALHIV, public policies, and laws among others. To illustrate, allocating funds to support intervention programs can affect their effectiveness. Concerning ART adherence, when fewer funds are allocated to hospitals, there may be understaffing of health workers and less stocking of ARVs, which results in patients missing medicine. For LMICs, poverty is an important structural factor that has undermined many efforts against HIV including ART adherence. Ssewamala and colleagues have shown that family-level asset-based economic strengthening interventions are efficacious in improving ART adherence and viral suppression (Bermudez et al., 2018; Ssewamala et al., 2020). Against this background, in this dissertation, household asset ownership was included as a potential predictor in the model to predict the risk of virologic failure (**Aim 2**).

In conclusion, taken as a whole, the three theories including the *Health Belief Model, Asset Theory*, and the Socioecological Model provide a robust theoretical foundation for understanding and addressing the aims and questions in the proposed dissertation. These theories

shed light on the complex interplay of individual perceptions, barriers, and assets, offering insights into the mechanisms through which interventions can effectively promote adherence and improve long-term outcomes. By utilizing these theories, this dissertation aimed to contribute to the body of knowledge surrounding ART adherence among ALHIV and inform evidence-based interventions that can enhance their well-being and quality of life.

Conceptual Framework

The theoretical framework, shown in **Figure 3**, is based on an integration of the three complementary theories discussed above—the *HBM*, *Asset Theory,* and the *socio-ecological model*. Each theory provides unique insights into different aspects of the dissertation.

The primary hypothesis of this dissertation centers around financial constraints as the main barriers to attaining and maintaining good ART adherence. Hence, by increasing the household's financial stability, the EE intervention could improve ALHIV's engagement with the healthcare system and improve treatment adherence. Specifically, we hypothesized that the EE intervention would have a positive impact on ART adherence, both directly and indirectly by improving the mediators, including *barriers to health care*, *adolescent social transition,* and *adherence self-efficacy,* which in turn improve the outcomes. In turn, the improved mediators would have a positive effect on the study outcomes.

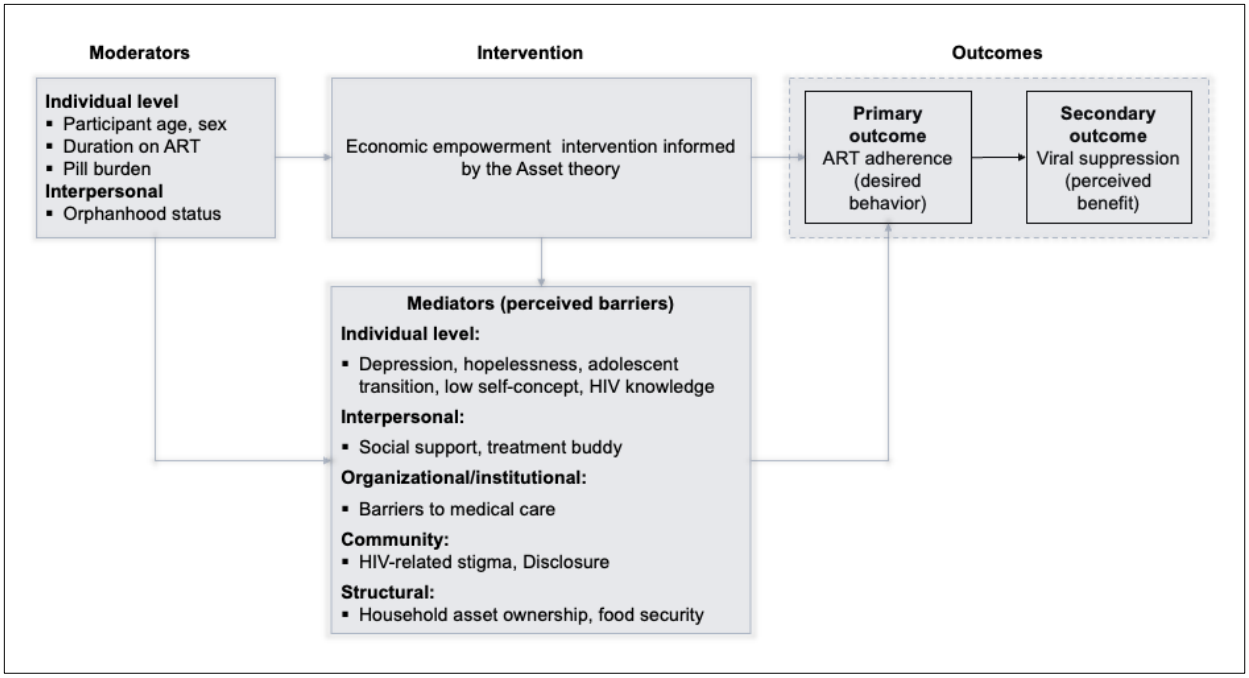

Figure 3: Conceptual Framework for the Proposed Dissertation

The moderators, classified according to the *socioecological model* influence the intervention effect on the mediators and the outcomes but also directly influence the mediators. In addition, the moderators have an association with both ART adherence and viral suppression. Hence, these moderators were included as potential predictors in the model to predict virologic failure **(Aim 2)**. As posited by the *asset theory*, EE interventions have beneficial effects in improving psychosocial and health outcomes, represented by the mediators and outcomes in this conceptual framework. The path from EE to the outcomes via the mediators explains the indirect effect of the intervention on ART adherence (**Aim 3)**.

As discussed in *the HBM*, one of the conditions for achieving a desired behavioral change is to recognize and overcome the barriers to achieving that change. By addressing the mediators (categorized according to the socioecological model—such as reducing depressive symptoms and overcoming the barriers to medical care) the EE intervention addresses the perceived barriers

to improving ART adherence (the desired behavioral change). Moreover, viral suppression is conceptualized as a benefit of ART adherence. Overall, the selection of the factors to include in this dissertation was informed by all three theories including the *HBM*, *Asset theory*, and the *socio-ecological model*.

Chapter 4: Methodology

Studies exploring ART adherence and viral suppression often exhibit methodological limitations usually arising from factors such as employing weaker study designs, lacking appropriate control groups, incorporating small sample sizes, and employing measures of outcomes that lack reliability. To contribute to the body of knowledge on ART adherence, this dissertation addresses the above limitations by employing robust methods on comprehensive data sourced from an ongoing longitudinal study. This chapter serves three purposes. ***First***, it describes the datasets that will be utilized, including the study design, eligibility criteria, and sample size that were employed in collecting the data. ***Secondly***, it outlines the variables that will be used in the analysis, presented according to the proposed aims. ***Finally***, this chapter elaborates on the statistical approaches that were used to analyze the data while answering the dissertation aims.

Description of the data source and sample

The dissertation utilized data from the *Suubi+Adherence* Study, a two-group cluster-randomized controlled trial. The study received funding from the Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD) under grant number 1R01HD074949–01 (Ssewamala, PI). Participants were recruited from 40 health clinics located in seven political districts (Bukomansimbi, Kalungu, Kyotera, Lyantonde, Masaka, Rakai, and Lwengo) in Southern Uganda. This region has an HIV prevalence of 12%, which is more than twice the national average of 5·4% (UAC, 2021). The study has been running since 2012.

Adolescents were included in the *Suubi+Adherence* study when they fulfilled the following criteria: 1) Aged 10 to 16 years; 2) Receiving medical confirmation of their HIV-positive status; 3) Aware of their HIV status; 4) Living within a family setting, as opposed to

institutionalized environments where distinctive characteristics and requirements may vary; 5) Being registered and receiving antiretroviral therapy (ART) from one of the collaborating clinics involved in the study. Health clinics were eligible for inclusion in the study if they possessed the necessary operational licensure and accreditation to administer ART services. Initially, a total of forty clinics were chosen for participation in the study. However, one clinic was subsequently excluded from the study due to its closure by district health officials, as it was found to lack a valid operational license, resulting in a final total of 39 clinics/healthcare centers.

Aims of the Suubi+adherence study

The primary objective of the study during its initial funding cycle (2012-2018) was to evaluate the impact of a family-based EE intervention on ART adherence among ALHIV. Following the initial five-year period, the Suubi+Adherence study secured additional funding for another five years (2020-2025). During this extended phase, the study focuses on the same cohort of ALHIV recruited in 2012, with the following objectives:

1. To examine the long-term impact of the Suubi+Adherence intervention on HIV viral suppression and key HIV treatment adherence outcomes for YLHIV.
2. To elucidate the long-term effects of the Suubi+Adherence intervention on potential mechanisms of change.
3. To qualitatively examine: a) multi-level factors affecting participants' maintenance of intervention benefits; and b) participants' experiences with the intervention, including multi-level factors that may have influenced their engagement with the program, as well as their decision-making regarding ART adherence.
4. To examine the long-term cost-effectiveness of the Suubi+Adherence intervention

Randomization and masking for the Suubi+Adherence study

Randomization was conducted at the clinic level by a Columbia University student who had no direct involvement in the study. Out of the 39 clinics initially selected, a 1:1 ratio was used to allocate them to either the intervention or control groups. As a result, the control group consisted of 19 clinics (n=344 ALHIV), while the intervention group comprised 20 clinics (n=358 ALHIV) after the randomization process was completed. To minimize the risk of contamination, all eligible ALHIV recruited from each clinic were assigned the same intervention—corresponding to the study group to which their clinic was assigned. ALHIV in the control condition received the standard of care for ALHIV, augmented with cartoon literature on ART adherence (Ssewamala et al., 2019). Conversely, ALHIV in the intervention group received the same standard of care and cartoon literature, along with the family EE intervention, which is described in detail below. Due to the nature of the intervention, it was not feasible to blind the ALHIV to their assigned groups.

Recruitment procedures.

Recruitment for the study took place between September 2013 and July 2014, during which a total of 702 ALHIV were enrolled. As a first step in the recruitment process, the medical staff at the clinic generated a list of eligible participants from the patient database. Subsequently, adult parents or caregivers of these eligible adolescents were introduced to the study by a healthcare provider during the adolescents' regular medical appointments. Caregivers who expressed interest in participating were contacted by the research staff, and verbal consent was obtained. Following this, a comprehensive process of written informed consent and participant enrollment was conducted. Upon enrollment, all participants underwent an interviewer-administered questionnaire, which typically lasted between 60 and 90 minutes. The questionnaire

aimed to gather detailed information pertaining to various aspects such as the participant's medical history, adherence to ART, socio-demographic factors, and psychosocial well-being. The structured interview format ensured that consistent and standardized data were collected from all participants. After recruitment and randomization, the participants received the intervention or standard of care, as detailed below.

The study interventions.

Control condition: As part of routine care, all ALHIV receive comprehensive HIV clinical and psychological care in accordance with the Uganda government Ministry of Health's recommended guidelines for childhood and adolescent HIV care (Health, 2020). These guidelines outline the standard of care that ALHIV should receive including **1) monthly reviews of ART adherence:** After enrolling into care, ALHIV undergo monthly reviews to assess their treatment response and adherence to ART. During these reviews, healthcare providers evaluate the effectiveness of the treatment and address any challenges or concerns that may arise; **2) Viral load monitoring:** As part of the routine HIV care, blood samples are collected from adolescents when they initiate ART to determine their baseline viral loads. Subsequently, viral load assessments are conducted at least once per year. This helps determine the effectiveness of the treatment in suppressing HIV; **3) Psychosocial support and adherence counseling:** Lay counselors, including PLHIV, referred to as expert clients, are stationed at each clinic to provide psychosocial support to ALHIV and their families, and to offer treatment adherence counseling. In addition, patients are usually provided with leaflets that contain information on ART adherence.

Despite the existence of these routine care guidelines, routine HIV care can be inconsistent, varying in frequency and quality. Hence, all ALHIV enrolled in our study

(including those in the control group) received a **bolstered standard of care (BSOC)**. In the BSOC, all participants received adherence counseling through a series of six one-hour sessions. This standardized approach ensured that ALHIV received consistent and comprehensive support. During these sessions, ALHIV were provided with age-appropriate information on various topics related to adherence. More details are provided in the protocol (Ssewamala et al., 2019).

Intervention condition: Intervention condition: Alongside the BSOC, participants in the intervention group received a **family EE intervention** spanning a duration of two years. This intervention consisted of three main components, including a youth development account (YDA), financial literacy training, and micro-enterprise workshops. To begin, a savings account was opened for each participant, which was initiated with an initial deposit of approximately 6 USD sponsored by the study. Subsequently, on a monthly basis, the study matched the amount saved by the participant, up to a maximum of around 10 USD, by depositing an equivalent sum into their account. Importantly, even after the intervention period, participants were encouraged to retain their accounts, with caregivers urged to continue making savings deposits. Furthermore, the intervention incorporated financial literacy and micro-enterprise workshops, which involved active participation from both the adolescents and their family members. These workshops comprised a series of up to eight sessions, focusing on topics such as initiating a micro-enterprise, effective financial management, setting short- and long-term goals, and the fundamentals of starting a business.

Ethical considerations.

Makerere University School of Public Health Research and Ethics Committee (Protocol # 210) in Uganda, Uganda National Council for Science and Technology (UNCST, SS, 2969), the Columbia University Review Board (AAAK3852; 2012-2017), and the Institutional Review

Board at Washington University in St. Louis (IRB # 201704066; 2017-current) in the USA granted approval for the study. Before enrollment, all participants provided age-appropriate informed assent, which was duly documented. In addition, written informed consent was obtained from the parents/caregivers of the participants. Study staff underwent training in Good Clinical Practice (GCP) to ensure adherence to ethical standards The trial is registered at ClinicalTrials.gov, number NCT01790373.

Measures used in the dissertation.

Aim 1: Compare the performance of the measures of ART Adherence

Viral load

Viral load testing was done once every year. To perform the viral load test, blood samples were collected from each ALHIV, and were processed to determine their HIV RNA viral loads. The blood samples were collected using EDTA tubes, and the assays were conducted using the Abbott Real-Time HIV-1 RNA Assay PCR, version 5. Based on their viral loads, ALHIV were dichotomized into those that attained viral suppression and those with virologic failure. As recommended by the 2022 Uganda national HIV treatment guidelines, viral loads of 200 copies/ml or above will be considered virologic failure (Ministry of Health, 2022). Viral load collected at baseline were used for this aim.

Self-reported adherence

Due to the inherent biases that come with self-reports such as recall and social desirability biases, using one question to measure self-reported adherence overestimates adherence. Hence, to measure self-reported ART adherence, this dissertation used three questions—assessing the 30-day recall of missed does, rating of adherence, and rating the

adherence-related difficulties—adapted from Wilson's three-item self-reported adherence tool (Wilson et al., 2016). The three items are:

1. "*In the last 30 days, how many days did you miss at least one dose of your HIV medications?*" The expected response was the number of days (Range 0 to 30).
2. *In the last 30 days, how often did you take your HIV medicine in the way you were supposed to?* (1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Usually, and 5 = Always.)
3. *How hard is it for you to take your HIV medicines in the way you are supposed to?* (Responses ranged from 1 = Extremely hard to 5 = Not hard at all).

Responses from each item were linearized by converting the individual scores into a percentage. Specifically, for item 1, the percentage adherence was calculated by dividing the number of days on which participants took their ART by 30, and then converting it to a percentage. For items 2 and 3, the percentage adherence was derived by dividing the individual score by 5 and multiplying the result by 100. A mean percentage adherence score was calculated by adding the percentage adherence from each of the three items and dividing it by three.

Pill counts adherence.

Our research team implemented a structured protocol for unannounced pill counts. The RA first verified the participant's medication regimen. The participant was then asked to gather all medications from various storage points in their residence. These medications were organized and details such as prescription numbers, refill dates, and dispensed quantities were recorded. The interviewer then inquired about any changes in pill quantities since the last count and daily drug intake. Pills were subsequently counted using a designated pharmacist tray and cup in the participant's view, with the counting process repeated to ensure accuracy. Additionally, the

procedure accounted for medication changes based on prescription data. Adherence based on pill counts was then calculated as follows (Haberer et al., 2012):

$$\mathbf{A} = \left(\frac{(\mathbf{Pill\ count\ on\ previous\ visit} + \mathbf{Refill}) - \mathbf{Pill\ count\ on\ current\ visit}}{\mathbf{Expected\ number\ of\ pills\ taken\ during\ assessment\ period}} \right) * \mathbf{100}\%$$

While many participants are usually prescribed more than one drug type, only one drug was selected for adherence analysis. Specifically, a non-nucleoside reverse transcriptase inhibitor (NNRTI) was chosen, namely Nevirapine or Efavirenz, for individuals receiving first-line treatment. For those on second-line therapy, a protease inhibitor such as Ritonavir/Lopinavir was utilized. Previous studies have also employed the selection of an NNRTI drug to calculate adherence based on pill count (Okatch et al., 2016; Wu et al., 2014). Using a single drug—as opposed to all the different types of ARVs that a participant is taking—has several advantages. *First*, it provides consistency since all participants take at least one drug. *Secondly*, it simplifies the analysis and facilitates the interpretation of the results.

Electronic adherence monitoring (Wisepill adherence).

Starting at baseline, the *Suubi+Adherence* study provided 603 (out of the 702) ALHIV with a Wisepill adherence monitoring device (Haberer et al., 2010; Wisepill, 2021) connected to a mobile telecommunications network. Each time the adolescent opened the device, a signal denoted as "intake" was transmitted to a centralized server, indicating the consumption of a dose. Conversely, when the device remained unopened, it registered a "heartbeat" signal, signifying proper functioning without dose intake. A signal labeled as "none" was exclusively sent in cases of device malfunction. Daily adherence information from the participants' Wisepill devices was transmitted to us. Adherence behavior was coded, where a missed dose was assigned a value of 0 (if the registered signal is a “heartbeat”), and a taken dose was assigned a value of 1

(corresponding to the signal “intake”). To obtain monthly adherence rates, the daily adherence data were aggregated, and the number of doses taken every month was determined.

Some criteria were established to assess EM adherence—hence forth referred to as Wisepill adherence— while ensuring data accuracy. ***First***, in cases where the devices malfunctioned and registered the signal as "none," resulting entries were treated as missing adherence data. ***Secondly***, previous analysis of the available Wisepill data revealed that, during the first few days following device acquisition, a few ALHIV opened their Wisepill device multiple times per day, potentially driven by curiosity or excitement. Unfortunately, each device opening was erroneously recorded as a pill intake in the central database. To mitigate this problem, data from the first seven (7) days after acquiring the device was discarded for all the participants. Subsequently, on the few times that ALHIV opened the Wisepill device more than once for a prescribed dose, only the first opening was considered, and subsequent openings were disregarded. Similar criteria have been used to analyze adherence data based on EM (S. Kizito et al., 2022).

Aim 2: To develop and validate a model to predict the risk of virological failure.

The outcome variable for this aim was virologic failure, which was defined as viral load of <200 copies/ml. Informed by the Health Belief Model and previous risk prediction models in similar populations (Becker, 1974; Brathwaite et al., 2021; Champion & Skinner, 2008), the predictor variables that were included in the risk prediction model are shown below, classified according to the socio-ecological model:

Individual level factors

HIV stigma was measured using a 9-item scale, derived from the Berger stigma scale (Berger et al., 2001), that assesses for internalized stigma. The scale comprises statements reflecting the self-perceptions of HIV-positive patients. Examples of these statements included "*When people know I have HIV, I feel uncomfortable around them*," and "*I feel guilty about having HIV.*" The respondents used a four-item Likert scale (ranging from 1 = strongly disagree to 4 = strongly agree) to indicate to what extent they agreed with each of the statements (Cronbach's alpha = 0.76). The scale has been previously used to measure stigma in the same population (Nabunya et al., 2020). Higher scores indicate higher levels of HIV stigma.

Depressive symptoms were assessed using the Children's Depressive Inventory (CDI). A shortened version of the CDI, which contains fourteen (14) items was used for this study. The 14-item CDI is a condensed version of the original 27-item CDI. Both versions of the CDI are standardized self-report measures and have been extensively used for depressive symptom assessment (Ahlen & Ghaderi, 2017; Kovacs, 2015; Rivera et al., 2005; Traube et al., 2010). Research has indicated that the CDI scale is reliable and valid across a variety of cultural contexts (Sun & Wang, 2015). Each item on the scale presented three response choices, represented as numerical codes 0,1, and 2, signifying progressively increasing depressive symptom severity (Kovacs, 2015). A cumulative score was generated by adding up scores from the individual scores, with a theoretical range of 0-28, where higher scores indicated more severe depressive symptoms. Cronbach's alpha = 0.64.

To collect data on **hopelessness**, a 20-item Beck's Hopelessness scale (Beck et al., 1974) was used to measure hopelessness. Participants were prompted to respond to each of the items in the scale with either "True", coded as 1, or "False" coded as 0. Specifically, items evaluated how

pessimistic the participants were about their future. Sample items included "My future seems dark," and "The future seems vague and uncertain to me." Any items phrased in the opposite direction were reverse-coded, after which, scores from each item were added to generate a total hopelessness score, with higher values indicating more hopelessness (Cronbach's alpha = 0.73). The scale has been previously used in other studies in Uganda (P. Cavazos-Rehg, W. Byansi, C. Doroshenko, et al., 2021).

Self-concept was measured using a 17-item short version of the Tennessee Self-Concept Scale (which originally contained 100 items) (Fitts & Roid, 1964; Fitts & Warren, 1996). Each item had responses measured on a five-point Likert scale, ranging from 1 = "Always False" to 5 = "Always True." Sample items included "*I like the way I look*," and "*I feel good most of the time.*" After reverse-coding items that were phrased in the opposite direction, the participants' responses from each item were added together to generate a total self-concept score (Cronbach's alpha = 0.76).

The adherence self-efficacy scale, comprising twelve items, was used to evaluate the adolescents' **adherence self-efficacy**—the belief in their ability to follow the prescribed ART routines (Johnson et al., 2007). The items asked the adolescents to rate their confidence in achieving tasks related to ART adherence, on a scale of 1 to 10, with higher scores indicating greater self-efficacy. Sample items included "*In the past one month, how confident were you that you can stick to your treatment schedule even when your daily routine is disrupted*," and "How *confident are you that you would stick to your treatment schedule even when doing so interferes with your daily activities.*" (Cronbach's alpha = 0.91).

Quality of life was measured in relation to school life using four questions adapted from the Pediatric Quality of Life Inventory version 4.0 (Varni et al., 1998). A sample item read "*I*

miss school because of not feeling well." A corresponding item for the ALHIV not in school reads "*When I was in school, I missed school because of not feeling well*." Each question had a five-point Likert scale response ranging from 1 = "Never" to 5 = "Always," resulting in a possible range of 4 to 20, with higher values signifying a better quality of life.

HIV/AIDS clinical knowledge was assessed using a series of nine (9) items, which were provided to the ALHIV probing their knowledge about HIV treatment. Participants were provided with items such as "*When a person is feeling healthy or their CD4 count is high, it is okay for them to stop taking their medication"* and "*The virus can become resistant if medication doses are missed*," and they were required to select whether the scenario was "true," "false," or they were "not sure." A score of 1 was awarded when the participant chose the correct option, or else they were awarded 0. An overall score was generated by adding up each participant's total points, with higher scores signifying more knowledge about HIV.

Other individual-level factors that were included in the predictive model include the participants' age, sex, orphanhood status, school enrolment, self-perceived personal health, whether the participant works to earn a payment, duration on ART, and the number of years the participant has spent while HIV positive.

Interpersonal level

Social support was assessed using a scale with 24 items, adapted from the Friendship Quality Scale (Bukowski, 1994). The ALHIV were provided with statements about other children and were asked to state how often the statements applied to them. Sample items included "*Some kids have a close friend who they can tell problems to*," and "*Some kids have classmates who like them the way they are*." Responses were on a five-point Likert scale ranging from 1 = "Never" to 5 = "Always." (Cronbach's alpha = 0.82).

Other interpersonal factors include household size, and whether the adolescent has a treatment buddy (a person who supports the ALHIV while undergoing HIV treatment and care).

Community level

HIV status disclosure was measured by asking ALHIV four questions to assess their openness about their HIV status. A sample question was "*How comfortable do you feel talking about your HIV status with other kids in school?*". All questions had responses on a four-point Likert scale ranging from 1 = "Very uncomfortable" to 4 = "Very comfortable." Scores from all items were summed up to generate a total disclosure score, with a higher score indicating more disclosure (Cronbach's alpha = 0.72).

Another community-level factor that was considered is the number of years that the participant has lived in the current residence (a proxy for mobility), which has been shown to affect access to medical care.

Structural level

At the structural level, factors related to poverty were examined including food security (the number of meals that the ALHIV takes per day) and household asset ownership. **Household asset ownership** was assessed using a 20-item asset index, which captured aspects such as the possession of a house, land, and various other forms of property, as reported by the families of the participating adolescents. Each item owned was coded with a 1, or else a score of 0 was awarded. A scale was generated from this asset index by adding up the total scores, with a theoretical range of 0 to 20, with higher values suggesting more asset ownership. (Cronbach's alpha = 0.76).

Aim 3: Mediators of the effect of an EE intervention on ART adherence.

The **outcome** for this aim was ART adherence, measured at year seven (7) of follow-up. A latent variable for ART adherence was created using six observed items including ART adherence measured using pill counts and five self-reported items. To obtain the five self-reported items, two items were added to the three questions that make up the Wilson self-reported adherence tool (Wilson et al., 2016). The two additional items were **1)** "*When was the last time you missed any of your HIV medication?*"—with responses from 1 "Never missed" to 6 "More than 3 months" and **2)** "*How hard is it for you to take your HIV medicines in the way you are supposed to*?", which was scored on a five point Likert scale ranging from "Extremely hard" to "Not hard at all." Adding more observed items was critical in improving the overall fit of the measurement model for ART adherence. No Wisepill data was collected in Suubi+Adherence R2 study, hence electronic adherence data was not available at year seven and was not considered in creating the latent adherence variable.

The main **predictor** variable for this aim was the family EE intervention—elaborated in the "interventions section" above—while the **latent mediators** were *barriers to healthcare*, *adolescent social transition,* and *adherence self-efficacy*. To preserve the temporal relationship between the intervention, mediators, and the outcome, the mediators that were used in the analysis are those that were assessed at year six, while adherence at year seven served as the outcome—as stated above. Data on the barriers to medical care and adolescent social transition was only collected in *Suubi+Adherence R2* starting at year six (6), hence, we did not have data on these mediators from the preceding years. Below is an elaboration of how the latent mediators were measured. The assessment for adherence self-efficacy was elaborated earlier under the measures for aim 2.

Barriers to medical care.

To understand the ALHIV's access (or lack of access) to medical care, we used the barriers to medical care scale (Kalichman et al., 1999). This was an eleven-item scale with each item having two responses—agree or disagree. To elaborate, ALHIV were asked to think of the reasons why they did not get the medical care they needed or that was recommended to them. Sample items on the scale included "*I was unable to pay for medical care,*" and "*I did not have transportation to medical care.*" Each response was coded as 0 if the ALHIV responded "agree" and 1 if "disagree" was selected. A total score was generated, by adding up the individual scores from each item, with a possible range of 0 to 11, with higher scores indicating more barriers to medical care.

Adolescent social transition.

Three domains of adolescent transition were considered including economic transition, which included money and work, residential independence, and healthcare transition readiness. To examine the participants' **money and work transition**, adolescents were asked whether they were employed at the time of the assessment. On the other hand, **residential independence** was ascertained from information about the participants' residential situation. Specifically, the participants were asked about their current residence, with responses including options such as own house, renting, and family house. **Healthcare transition readiness** was assessed using a 17-item scale transition readiness assessment questionnaire (TRAQ) (Wood et al., 2014). Items in this scale examined the participants' readiness to handle their daily lives and medication adherence. Sample items included "Do *you know what to do if you are having a bad reaction to your medication?*" and "Do *you arrange for your transportation to medical appointments?*" The items were scored on a five-point Likert scale ranging from 1 = "No, I do not know how" to 5 =

"Yes I always do this when I need to." Responses from each item were added to generate a total TRAQ score, with a theoretical range of 16 to 80. Higher scores indicated more healthcare transition readiness. Besides the mediators, we included covariates (measured at baseline) in the model including the participants' age, sex, and orphanhood status. However, for parsimony, these were excluded from the final model since they were not significantly associated with the intervention, mediators, or the outcome.

Data analytical approach

All descriptive analyses were conducted using Stata statistical software, version 18.0. Continuous variables were summarized using means and standard deviations or medians and interquartile range depending on the data distribution, while categorical variables were summarized with frequencies and percentages. Baseline characteristics were compared across the two study groups to ensure the effectiveness of the randomization. To compare the groups, while adjusting for clustering, survey data commands including *svy: regress* and *svy: tab* for continuous and categorical data were used, respectively. Analysis procedures specific to study aims are presented below.

Aim 1: Compare the performance of the ART Adherence measures.

To ensure that all adherence measures and viral loads were contemporaneous, measures that were collected within a one-month window were used. Specifically, baseline measures of adherence and viral load were considered for this analysis. Moreover, another advantage of using baseline data is that it eliminated any possibility of having a differential effect of the intervention on adherence for some participants in the intervention group compared to those in the control group. Below is a detailed description of the analysis for **Aim 1**.

Concordance and Kappa Statistics

Adherence based on each measure (SR, pill counts, and Wisepill) were categorized into poor (below 90%) and good adherence, based on recent literature (Byrd et al., 2019; O'Halloran Leach et al., 2021), which also aligns with the Uganda national guidelines (Health, 2020). A **kappa statistic** was then applied to assess the level of agreement (beyond chance) between the categorized adherence from the different pairs of adherence measures (Dettori & Norvell, 2020). Kappa was calculated as follows.

$$\boldsymbol{\kappa = \frac{P0 - Pe}{1 - Pe}}$$

Where **P0** is the observed proportion of agreement, and **Pe** is the expected proportion of agreement by chance. To control for the clustering of participants within clinics, cluster bootstrapping was employed in calculating the kappa statistics. A kappa value between 0 and 0.2 suggested slight agreement, 0.21 to 0.40 denoted fair agreement, 0.41 to 0.60 suggested moderate agreement, 0.61 to 0.80 suggested substantial agreement, and values above 0.80 represented almost perfect agreement (Dettori & Norvell, 2020).

However, the kappa statistic is sensitive to the prevalence of the condition being measured, with considerably poor agreement observed when the prevalence is either low or high. When faced with this situation, Gwet recommended the agreement coefficient (AC_1) as an alternative to kappa statistic (Gwet, 2008). Given that most ALHIV reported good ART adherence (high "prevalence"), in addition to the Kappa statistic, the AC_1 was also calculated for this study.

Bland-Altman analysis.

To further examine the agreement between the continuous adherence measures (SR, pill counts, and Wisepill), separate Bland-Altman plots were constructed for each pair of measures. These graphs plot the difference in the percentage adherence between two methods (bias) against the mean percentage adherence (magnitude). Bland-Altman plots not only show the magnitude of disagreement but also highlight the systematic bias between measures, which cannot be revealed with the kappa statistics. When using Bland Altman statistics to compare two methods A and B, the expected measurements by method B can easily be predicted from the observed measurements by method A, by adding the estimated bias. However, this is only applicable when there is constant bias across the two methods. In cases where there is increasing or reducing bias, a regression-based bias is generated by regressing the residuals in the Bland Altman plot against the mean of the two methods (Carstensen, 2011). This regression model is then used to predict measurements of method B from those of method A. The same approach was employed in this dissertation having observed a diminishing bias as the mean ART adherence increased.

Predictive Analysis.

The accuracy of each adherence measure (the "test") to predict viral suppression (the "disease") was initially examined by determining their **sensitivity and specificity.** *Sensitivity* was defined as the proportion of adolescents who were identified as good adherers based on the adherence measure out of all those with non-detectable viral load. Similarly, *specificity* was the proportion of adolescents that the adherence measure identified as having poor adherence out of all adolescents with detectable viral load. In addition, the unadjusted **Area Under the Receiver Operating Characteristic Curve** (AUC) was also computed. However, after observing low AUC values (<0.6) for all three adherence measures, covariate-adjusted bootstrapped (1000

replicates) Receiver Operator Characteristic Curves (ROC) and AUCs were generated to account for the effect of selected additional factors on the association between ART adherence and viral suppression. AUC below 70% showed poor discriminatory ability of the test, while values of 70% to 80%, 80% to 90%, and above 90% represented acceptable, excellent, and outstanding test performances, respectively (DW Hosmer Jr, 2013).

The capacity of each adherence measure to predict viral suppression was further investigated using **multilevel logistic regression models**. In running these models, the clinic ID was included in the model using *vce* and *robust* to adjust for the clustering of the participants within clinics. A separate regression model was fitted for each adherence measure, in which the adherence measure was included as an independent predictor, with viral suppression status being the dependent variable. Factors including the participants' age, gender, depressive symptoms, duration of ART, and the number of pills taken per day were also included in the models as covariates. Odds ratios were reported (alongside their Eicker-Huber-White cluster-adjusted confidence intervals). The approach of using logistic regression to test the predictive capacity of test measures on outcomes including viral suppression has been previously used (Da et al., 2018; Forman et al., 2022; Orrell et al., 2017).

Aim 2: To develop and validate a model to predict the risk of virological failure.

Model development.

Initially, potential predictors to be used in the model were examined to ensure they met the model assumptions, such as linearity and no outliers. Variables that demonstrated a non-linear relationship with virologic failure were manipulated in various ways including log transformation (depressive symptoms and years spent while HIV positive), inverse

transformation (HIV stigma), square root transformation (social support), and restricted cubic splines, which was used for HIV knowledge, and the number of years spent at the current address.

To improve the model prediction and avoid overfitting, the **least absolute shrinkage and selection operator (LASSO) penalized regression** was used to select the subset of predictors that contributed the most in predicting virological failure (Alonzo, 2009). LASSO performs data shrinkage by applying a penalty factor (λ) to the regression coefficients. The best penalty factor (λ) was selected using 10-fold cross-validation with bootstrapping. In this method, the data is split into 10 portions (folds) then a model is developed using 9 folds, while the fold that is left out will be used as testing data. This process is then repeated ten times with each time leaving out a different fold of data, until all folds have been used. Applying the penalty results in shrinking the small coefficients to zero hence eliminating the least contributing variables from the model. The penalization also ensures that very large coefficients are shrunk to lesser values. This way, penalization avoids extreme predictions.

The next step involved determining the contribution of each variable to virologic failure and calculating the individualized risk score, which represents the log odds of virologic failure for each participant. The equation for calculating the individualized risk of virologic failure is shown below (Alonzo, 2009).

$$\mathbf{Risk} = \frac{\mathbf{1}}{\mathbf{1} + \mathbf{e}(-\mathbf{riskscore})}$$

However, regression coefficients obtained directly from the selected variables retained in a LASSO model are usually biased and cannot be used to accurately compute individualized risks (Belloni et al., 2014). To **obtain debiased estimates**, lasso inference models were used.

Specifically, a **cross-fit partialing out logistic regression model** was run using the *xpologit* command to generate regression coefficients for calculating individualized risk for virologic failure(Belloni et al., 2014; Wooldridge, 1996). In fitting this model, the variables retained in the LASSO model were included as predictors, while the rest of the variables (initially eliminated by the LASSO model) were added as control variables.

Model performance and internal validation.

The next step involved assessing the performance of the risk prediction model through determining for the discrimination and calibration. ***Discrimination*** was assessed by computing the concordance (*c*) statistic (AUC). It indicated the ability of the model to differentiate between ALHIV with virologic failure versus those who achieved viral suppression. The AUC was obtained by plotting a ROC curve with sensitivity and 1-specificity on the y and x axes. AUC values between 50% and <70% suggest poor discrimination, while AUC values of 70% to <80%, <80% to 90%, and >90% indicate acceptable, excellent, and outstanding performance of the model in discriminating between ALHIV with and without virologic failure. The 95% confidence intervals for the AUC were also generated using the bootstrapped resampling method. ***Calibration*** involved determining the agreement between model-predicted and the observed risk of virologic failure. A calibration plot was generated using the *pmcalplot* package, with the predicted risk of virologic failure on the *x*-axis, and the observed risk on the *y*-axis. In a calibration plot, perfect prediction follows a straight line at 45^0 with a calibration slope of 1 and intercept through 0.

While assessing the model performance, cluster (clinic) bootstrapping with 1000 replicates was performed to further correct for overfitting (hence improve our model performance) using optimism-corrected measures, including the *c* statistic and calibration slope.

Optimism correction through bootstrapping is achieved by replicating model development process (including variable selection) in each of the bootstrap samples to generate a model (bootstrap model). This bootstrap model is then be applied to the same bootstrap sample (to obtain the apparent performance) and to the original dataset to obtain test model performance. Optimism is then calculated as the difference in validation parameters between the model from the original data and the model applied to the bootstrapped sample. A pooled optimism is calculated for all the models from the bootstrap samples. The obtained optimism estimate is subtracted from the estimates obtained in the original data to generate optimism-corrected c-statistic and calibration slope. Statistical significance was set at a p-value of <0.05. Throughout the analysis, the clinic ID was included in the model to adjust for clustering due to clinic membership.

Aim 3: Mediators of the effect of an EE intervention on ART adherence.

Mplus software, version 8.10 was used to examine the pathways through which the EE intervention exerted its influence on ART adherence. Specifically, the direct, indirect (through *barriers to medical care*, *adolescent social transition,* and *adherence self-efficacy*), and total effect of the EE intervention on ART adherence were assessed. Structural equation modeling (SEM) was employed, using full-information maximum likelihood estimation (default), while applying the *cluster* command to address clustering at the clinics in the data. The models were fitted such that the temporal order of events was preserved. That is, the intervention (first two years) preceded the mediators (year six), which also preceded the outcome (year seven). While longitudinal mediation analysis performed using a cross-lagged autoregressive approach yields the least biased estimates—since it includes mediator and outcome data collected at all time points (Mitchell & Maxwell, 2013)—this approach was not feasible in this study since data on

the mediators was collected starting from year six. For this reason, a sequential mediation analysis was used, which still maintains the temporal order of events.

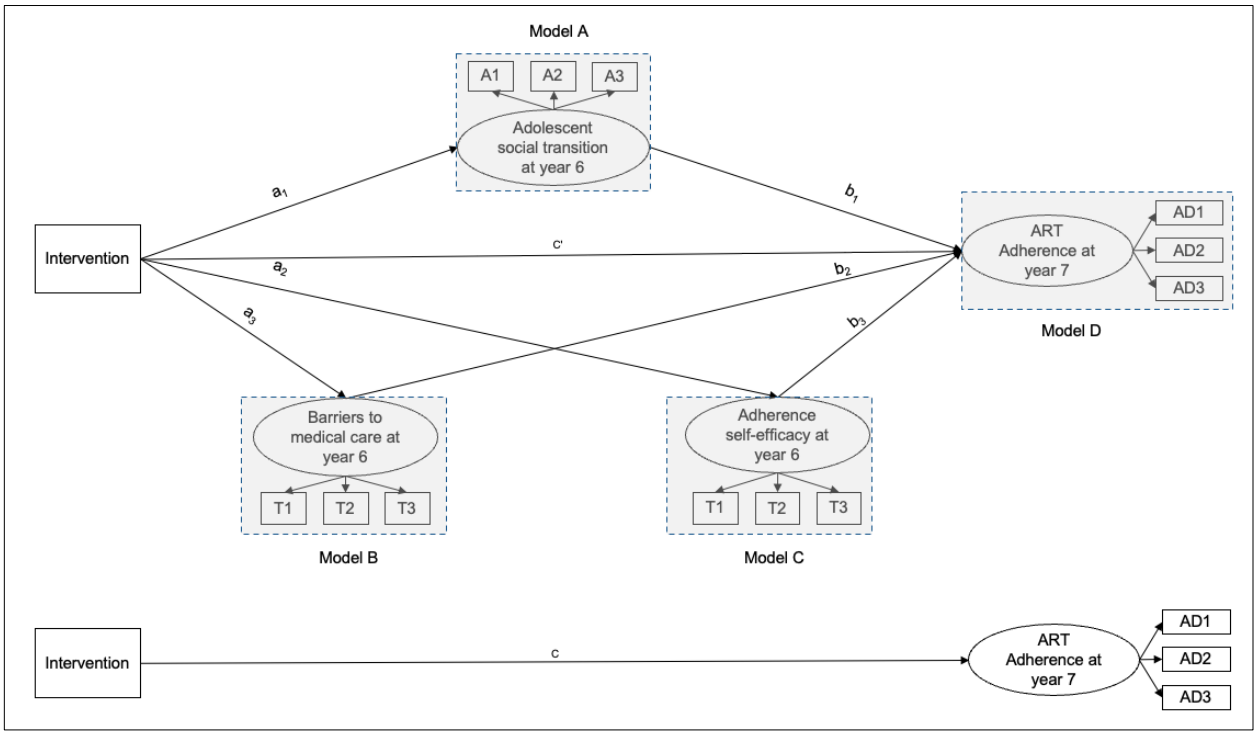

Figure 4: Diagram showing the structural equation model.

The diagram shows pathways between the economic empowerment intervention and ART adherence seven years later among ALHIV. Models A, B, and C have been simplified for illustration purposes. Barriers to medical care is a latent variable measured using 11 indicators; while adolescent social transition, adherence self-efficacy, and ART adherence are latent variables generated from 18, 12, and six indicators, respectively.

Initially, separate **measurement models** (that is; barriers to medical care, adolescent social transition readiness, adherence self-efficacy, and ART adherence) were run, using Confirmatory Factor Analysis (CFA), to evaluate the factor structure for each latent variable used in the structural model. Then a **structural model** was fitted by combining the measurement models with the intervention. As shown in **Figure 4**, the effect of the intervention on the

mediators is represented by paths a_1 *to* a_3, while paths b_1 *to* b_3 represent the effect of the mediators on ART adherence (Gunzler et al., 2013; Hair et al., 2021).

The **indirect effect** of the intervention on ART adherence was obtained as the product of paths, for example, a_1 and b_1, (a_1*b_1). The **direct effect**, represented by *c'* was the effect of the intervention on ART adherence conditional on (i.e., controlling for or in the presence of) the mediators. The **total effect** of the intervention on ART adherence, denoted *c*, was the sum of the direct and indirect effects (Gunzler et al., 2013). In the SEM, age, and gender were included as control variables. The standardized coefficients, β, and their standard errors were reported. A significance level of $p = 0.05$ was considered.

Model fit evaluation was done for each measurement model and for the structural model. An overall model chi-square statistic was computed to determine the exact global model fit, with a non-significant p-value denoting exact model fitness. Because the chi-square test is sensitive to small sample sizes and violations of the assumption of multivariate normality, a significant p-value for chi-square was not considered a bad model fitness. Instead, other approximate model fit indices were assessed, including the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Square Residual (SRMR). As recommended by Hu and Bentler, meeting one of the following two criteria indicated satisfactory approximate model fitness: (a) CFI ≥ .95 and SRMR ≤ .08 or (b) RMSEA ≤ .06 and SRMR ≤ .08 (Hu & Bentler, 1999).

Power and sample size considerations

In developing the risk prediction model, the sample size was determined based on the events per variable (EPV) ratio (Alonzo, 2009). In the EPV ratio, the "event" represents the

number of outcomes, while the "variable" refers to the total number of variables (including dummies for categorical variables) in the model. A rule of thumb is that an EPV of 10 or more is necessary to obtain reliable model estimates. Lower EPV values can lead to issues such as overfitting, biased results, and unstable model estimates—which can significantly vary with small changes in sample size. In our previous work, we found that 278 (39.6%) ALHIV in the *Suubi+adherence* study experienced virologic failure at baseline (S. Kizito et al., 2022). With 231 events out of 702 observations, our risk prediction model could accommodate up to 24 variables. Therefore, the risk prediction model has sufficient sample size to provide reliable estimates.

SEM is highly dependent on sample size and is sensitive to small sample sizes (Wang & Wang, 2019). When models rely on small sample sizes, they often encounter issues such as failure to converge, poor model fit indices, and incorrect parameter estimates. Despite ongoing debates, there is currently no consensus on the appropriate sample size for SEM-based analyses. As discussed by Wang et al., one approach to determining an acceptable sample size is based on the N:*q* ratio, where N represents the number of observations and *q* represents the number of free parameters (Wang & Wang, 2019). A commonly accepted guideline suggests that the N:*q* ratio should be at least 5:1, which was met using our sample size. Moreover, Wang et al. suggest that a sample size of 200 is sufficient to provide reliable SEM estimates. Hence, via this criterion, with data from 576 ALHIV, the study was sufficiently powered to address **aim 3**.

Missing data

For **Aim 1** (comparing the performance of adherence measures), the analysis was limited to participants with complete data on the adherence measures and viral load. Overall, 702 participants had complete data on self-reported adherence, while 455 and 602 participants had

complete data on adherence based on pill count and Wisepill methods, respectively. To examine the bias due to excluding some participants with missing data, the baseline characteristics between the 455 participants who had complete data on pill counts versus those who had missing data were compared. The two groups were comparable (see **supplementary Table 1**).

The risk prediction model **(Aim 2)** was developed using the 532 participants who had complete data on all variables. As such, baseline characteristics were compared between participants that were included in developing the models versus those that were excluded (See **supplementary Table 3**). There were no significant differences in baseline characteristics across the two groups of participants. Nonetheless, Ewout (2009) provides caution when using complete case analysis (involves discarding records with missing data on any of the variables) or available case analysis (utilizes available data but ignores missing data) (Alonzo, 2009). These approaches can lead to incorrect regression coefficients and biased risk prediction models. He recommends performing the analysis using complete data generated through multiple imputation (MI) or performing MI as part of the sensitivity analysis. Analyzing MI datasets can result in more reliable models. Therefore, sensitivity analysis was done using data that was generated through multiple imputation using chained equations (MICE). During multiple imputation, clinic ID was included in the imputation model to account for data clustering at the clinic level. A total of 10 MI datasets were generated. A limitation of multiple imputation in Stata is that there is no provision for LASSO regression to pool regression estimates from the MI datasets. Therefore, after generating the MI datasets, the *mi extract* command was used to store separate complete MI datasets. LASSO models were then performed on each of the MI datasets and determined the variables that were consistently selected across the datasets **(Supplementary Table 4)**.

Specific to the **third aim** of this dissertation, out of the 702 ALHIV participants recruited at baseline, a total of 576 participants were retained at year seven, providing outcome data for aim 3— ART adherence. This represented an attrition rate of <20% over a decade. Despite the attrition, the remaining sample size was still large enough to test the hypotheses of interest for **aim 3**, as earlier discussed in the section on power and sample size considerations.

Chapter 5: Results

This chapter presents the detailed findings from the dissertation study, organized according to the study's specific aims. Initially, an overview of the baseline sociodemographic, behavioral, psychological, economic and treatment related characteristics of the participants is provided, organized according to the levels of the socioecological model. The baseline characteristics are presented as a summary for the entire sample, as well as a comparison between the two study arms.

Following the presentation of the baseline characteristics, the chapter presents the results specific to each study aim, starting with comparing the performance of the different adherence measures **(Aim 1)**, followed by results from the developing and validating a risk prediction model **(Aim 2),** and finally examining the mediators of the effects of the economic empowerment intervention on ART adherence **(Aim 3)**. At the end of the results for each aim, a sensitivity analysis section is included to assess the robustness of the findings. The sensitivity analysis results evaluate whether the main results hold under various assumptions and conditions, such as using imputed data versus complete case analysis, comparing demographic characteristics between participants included in the analysis versus those excluded, applying alternative statistical models, and examining the impact of different methodological choices. Below is a detailed presentation of the results.

Description of the Participant Characteristics

The participant flow during the *Suubi+Adherence* study is shown in the consort diagram, presented as **supplementary Figure 1**. At baseline, the mean age of the ALHIV was 12.4 years

(SD = 1.98), and more than half (56.4%) were females. Details of the baseline characteristics are summarized in **Table 1**.

Table 1: Baseline characteristics of 702 adolescents living with HIV in Uganda.

	Mean (SD)/ number (Percentage)		
Characteristics	**Control**	**Intervention**	**Total**
Individual level			
Participant age (min/max: 10 to 16)	12.4 (1.97)	12.5 (1.98)	12.4 (1.98)
Sex assigned at birth (Female)	193 (56.1)	203 (56.7)	396 (56.4)
The participant is in school	301 (87.5)	312 (87.2)	613 (87.3)
Adolescent works for pay	33 (9.59)	32 (8.94)	65 (9.3)
HIV stigma (min/max: 9 to 35)	18.4 (5.95)	18.3 (5.90)	18.6 (5.93)
Depressive symptoms (min/max: 0 to 20)	5.2 (3.69)	5.2 (3.84)	5.2 (3.76)
Adherence self-efficacy (min/max: 20 to 120)	95.2 (23.5)	93.4 (23.0)	94.3 (23.3)
Quality of life (min/max: 4 to 20)	14.4 (3.49)	14.1 (3.64)	14.2 (3.56)
HIV/AIDS clinical knowledge (min/max: 0 to 9)	6.0 (2.00)	6.0 (1.97)	6.0 (1.98)
Duration (years) with HIV (min/max: 0 to 16)	3.7 (2.97)	3.6 (3.12)	3.64 (3.05)
Duration (years) on ART (min/max: 0 to 16)	3.9 (3.22)	4.0 (3.51)	3.94 (3.36)
Interpersonal level			
Family cohesion (min/max: 12 to 40)	31.4 (6.72)	32.1 (6.75)	31.8 (6.74)
Social support (min/max: 56 to 120)	87.6 (14.3)	89.2 (13.9)	88.4 (14.1)
Orphanhood status			
Non-orphan	115 (33.9)	131 (37.3)	246 (35.7)
Single orphan	129 (38.1)	133 (37.9)	262 (38.0)
Double orphan	95 (28.0)	87 (24.8)	182 (26.4)
People in the household (min/max: 2 to 18)	5.78 (2.46)	5.70 (2.65)	5.74 (2.56)
Community level			
Disclosure of HIV status (min/max: 4 to 16)	7.3 (3.08)	7.6 (3.24)	7.5 (3.16)
Years at current residence (min/max: 0 to 16)	8.5 (4.51)	8.6 (4.58)	8.5 (4.54)
Structural level			
Household asset ownership (min/max: 1 to 20)	10.9 (3.38)	10.6 (3.69)	10.8 (3.54)

ART: Antiretroviral therapy. SD: Standard deviation.

The majority, 87.3%, were enrolled in school, while almost one-tenth (9.3%) worked to earn a payment. The average duration of time the ALHIV have been taking ART was 3.9 years (SD = 3.36). Regarding the household structure, each household had an average of six people (SD = 3). Only 35.7% (n = 246) of the participants were not orphans, while 38% (n = 262) had lost one of their parents.

At the community level, on average, each ALHIV had lived in the current residence for 8.5 years (SD = 3.54). On assessing household asset ownership, a mean asset index score of 10.8 (SD = 3.54) was found. Overall, the baseline characteristics were similar across the two study groups.

Aim 1: Compare the performance of the measures of ART Adherence.

Results for this aim are based on a complete case analysis of baseline data, with multiple imputations used for sensitivity analysis. The analysis was split into two main sections. ***First***, the three adherence measures were compared to determine their relative performance in measuring ART adherence. ***Second***, the accuracy of each adherence method in predicting viral suppression was determined.

The median ART adherence measured with self-reports, pill counts, and Wisepill measures was 98.9% (IQR: 86.7% – 100.0%), 100.0% (IQR: 100.0% – 100.0%), and 98.0% (IQR: 90.2% – 99.7%), respectively. However, on categorizing the ALHIV into good (attained ≥90% adherence) and poor adherers (Byrd et al., 2019; Ministry of Health, 2022), only 73.0% (95% CI: 69.6 – 76.2) of the ALHIV reported good ART adherence. In contrast, the proportion of ALHIV found to have good adherence measured by pill counts and Wisepill were 87.4% (95% CI: 83.7 – 90.4) and 75.6% (95% CI: 72.0 – 78.9), respectively.

Agreement between the measures: Kappa and AC_1

On pairwise comparisons, there was moderate agreement between the three methods (Refer to **Table 2**). Specifically, the agreement between self-reports and pill counts was 65.35%, while the agreement between self-reports and Wisepill, as well as pill counts versus Wisepill were 63.39% and 68.24%, respectively.

Table 2: Agreement between the adherence measures.

Adherence measures	Observed agreement	Expected agreement	Kappa	AC_1	P value
Self-report vs. pill counts	65.35	66.59	-0.037	0.489	0.791
Self-reports vs. Wisepill	63.39	62.03	0.036	0.410	0.188
Pill counts vs. Wisepill	68.24	69.14	-0.029	0.545	0.731

AC_1: Agreement coefficient.

The corresponding kappa statistics showed that there was **poor agreement between the adherence measures**, with absolute values less than 0.10. Since the kappa statistic is highly dependent on the prevalence of the condition being measured—as was discussed in the methods section—the agreement coefficient (which adjusts for the effect of the high prevalence) was also computed (Gwet, 2008). The agreement coefficient, AC_1, showed moderate agreement between the measures of adherence, ranging between 0.410 (self-report versus Wisepill) and 0.545 (pill counts versus Wisepill). Not surprisingly, none of the observed agreements were beyond chance, as evidenced by the non-significant p values.

Agreement between the measures: Bland Altman

Further pairwise analyses were conducted using Bland Altman plots to understand better the agreement—including the bias—between the three adherence measures **(Figure 5).** When the self-reported adherence was compared to Wisepill adherence, it was observed that the two **measures showed considerable discrepancy, especially when the mean adherence between**

the two measures was low. However, this disagreement diminished as the mean adherence increased. The corresponding bias (denoted by the dashed red line in **Figure 5**) also diminished with increasing adherence. Similar results were observed when pill count adherence was compared to Wisepill adherence.

Regarding the comparison between self-report and pill count adherence, there was constant bias at the different mean adherence levels of the two measures. However, like the preceding comparisons, more discrepancy was observed between these two measures when the mean adherence was low but reduced with increasing adherence.

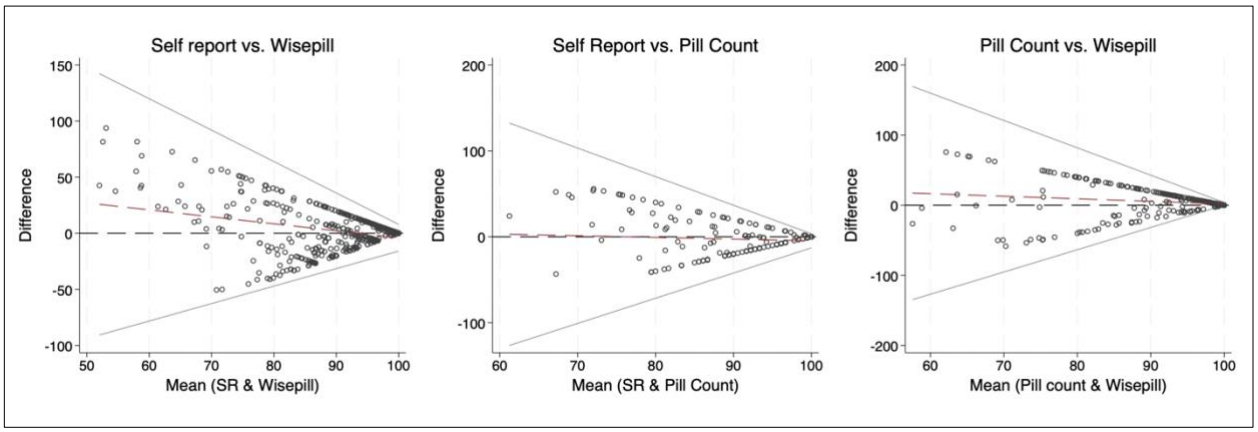

Figure 5: Bland Altman plot comparing the agreement between measures of ART adherence.

In the figure above, the y-axis includes the difference in adherence between a pair of adherence measures, while the mean for the two measures is plotted on the x-axis. The red dashed line represented the regression-based bias between the two methods. The two solid converging lines on either side of the bias line represent the lower and upper limits of agreement.

On close examination of all the three Bland Altman plots, there was even distribution of the data points on both sides of the reference line (horizontal line through 0), which suggested that **none of the measures over-estimated ART adherence** compared to the other measures. After observing funneling Bland Altman plots (proportional bias), the predicted residuals were

regressed against the mean adherence values for each pair of adherence measures to compute the regression-based bias for estimating adherence across the respective pair **(Table 3)**. While there was no statistically significant change in bias between self-report and pill counts, significantly decreasing bias was found between SR versus Wisepill, and pill counts vs. Wisepill. The significant bias across the latter two comparisons suggested that the **bias significantly reduced as the observed ART adherence increased.**

Table 3: Bias in measuring ART adherence among ALHIV in Uganda using three methods.

	SR vs. Pill count β (95% CI)	**SR vs. Wisepill β (95% CI)**	**Pill count vs. Wisepill. β (95% CI)**
Bias	-0.196 (-0.407, 0.014)	**-0.621 (-0.767, -0.474)**	**-0.363 (-0.566, -0.160)**
Residuals	-1.596 (-1.692, -1.500)	-1.111 (-1.202, -1.020)	-1.805 (-1.910, -1.701)
Lower LOA	-306.1 + 2.932 x mean	-171.7 + 1.557 x mean	-317.5 + 3.175 x mean
Upper LOA	336.1 – 3.325 x mean	287.9 – 2.779 x mean	394.0 – 3.902 x mean

CI, Confidence Intervals; LOA, Limits of agreement; SR, Self-report.

To demonstrate the practical use of regression-based bias, Wisepill adherence can be estimated using SR adherence by adding bias between SR and Wisepill to the observed SR adherence data. The bias for this computation is obtained as follows. Bias = -0.621*mean adherence (between SR and Wisepill).

Accuracy of adherence measures in predicting viral suppression.

On determining the viral suppression levels, the results showed that at baseline, among the 702 ALHIV, only 471 participants had viral loads lower than 200 copies/ml, representing low **viral suppression levels of 67.1% (95% CI: 63.5% – 70.5%)**. **Table 4** presents the sensitivity and specificity of the three adherence measures (self-reports, pill counts, and Wisepill) in predicting viral suppression. The results showed generally high sensitivity (especially with lower

adherence) and low specificity for each test in predicting viral suppression. The unadjusted AUC for self-report, pill count, and Wisepill adherence measures were found to be low, at 0.538 (95% CI: 0.495 – 0.581), 0.498 (95% CI: 0.456 – 0.541), and 0.521 (95% CI: 0.472 – 0.571) respectively.

Table 4: Sensitivity and specificity of adherence measures in predicting viral suppression.

	Self-Report		Pill Counts		Wisepill	
Adherence	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
≥40	100.0%	0.00%	100.0%	0.00%	97.8%	1.05%
≥50	99.6%	0.00%	98.4%	2.38%	97.3%	3.68%
≥60	98.7%	0.43%	97.3%	3.97%	94.9%	6.84%
≥70	96.6%	3.90%	95.3%	5.56%	91.5%	10.5%
≥80	87.0%	18.6%	91.8%	9.52%	87.4%	13.7%
≥90	74.9%	30.7%	87.1%	11.9%	76.0%	25.3%
≥95	54.9%	49.4%	82.8%	15.9%	64.3%	38.4%

When applying the threshold for adequate adherence (≥ 90%), the self-reported method accurately identified adherence in 60.3% of the participants. Pill count and Wisepill, in comparison, correctly classified 60.7% and 56.2% of the participants, respectively.

Following the low unadjusted AUCs, covariate adjusted AUCs were computed, as was discussed in the methods section. **Figure 6** shows the covariate-adjusted bootstrap corrected ROC curves and their corresponding AUCs. The results showed low AUCs (although slightly higher than the unadjusted AUCs) for the three measures, indicating limited discrimination power for all three adherence measures in predicting viral suppression. Specifically, self-reported adherence yielded an AUC of 0.616 (95% CI: 0.547 – 0.691), while pill counts and Wisepill measures had AUCs of 0.560 (95% CI: 0.471 – 0.607) and 0.570 (95% CI: 0.520 – 0.612), respectively.

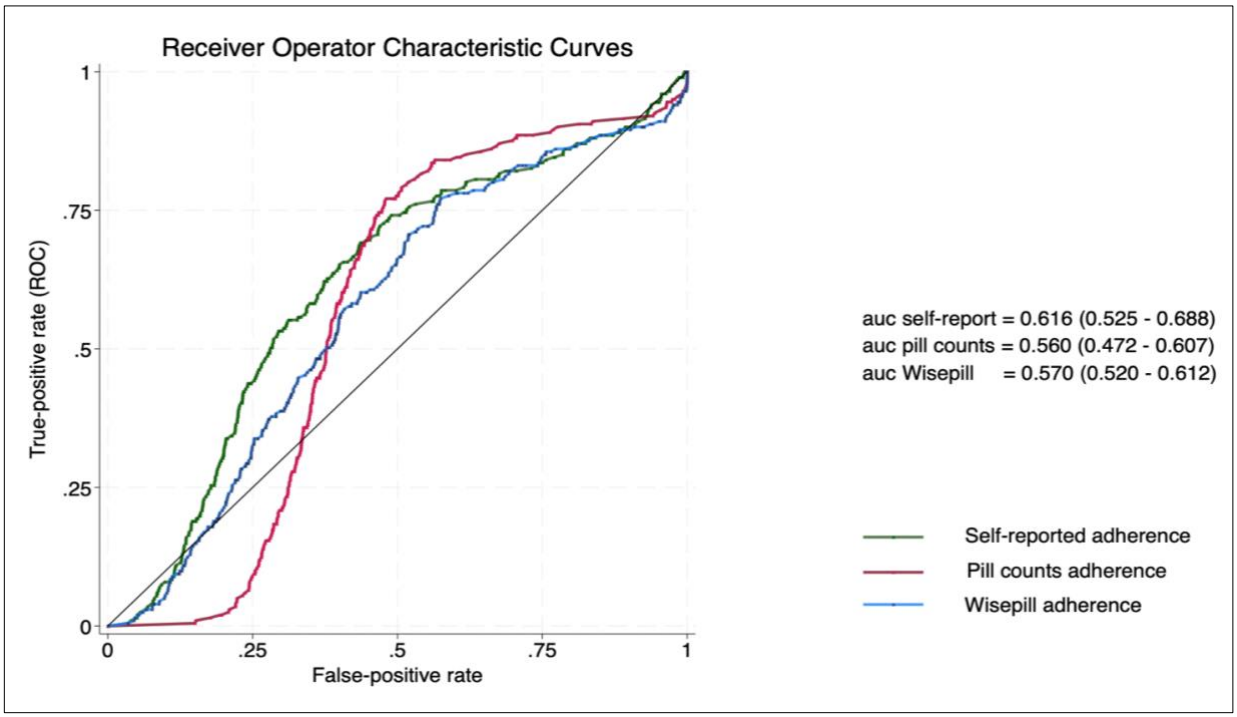

Figure 6: Receiver Operator Characteristic (ROC) Curves for viral suppression prediction.

Further analysis involved fitting multilevel logistic regression model (**Table 5)**, to determine the association between the measures of adherence and viral suppression. The results showed that **self-reported adherence was significantly associated with viral suppression**, with OR = 2.16 (95% CI: 1.25 – 3.81), p = 0.006. In other words, ALHIV that achieved adequate ART adherence—that is, adherence ≥ 90% (Byrd et al., 2019; Ministry of Health, 2022)—had 2.16 times the odds of attaining viral suppression than those reporting poor ART adherence.

On the other hand, neither pill counts nor Wisepill were a significant predictor of viral suppression. The results also showed that elevated depressive symptoms were consistently associated with poor ART adherence, measured using all three adherence measures.

Table 5: Association between ART adherence and viral suppression among 702 ALHIV.

	Self-reports OR (95% CI)	**Pill count. OR (95% CI)**	**Wisepill OR (95% CI)**
ART adherence (≥ 90%)	**2.16 (1.25 – 3.81)***	1.29 (0.77 – 2.16)	0.99 (0.74 – 1.33)
Participant age	0.97 (0.81 – 1.16)	0.98 (0.86 – 1.13)	0.96 (0.85 – 1.08)
Female sex	1.30 (0.71 – 2.36)	0.85 (0.49 – 1.48)	1.04 (0.64 – 1.68)
Orphanhood status			
Single orphan	0.67 (0.36 – 1.25)	0.74 (0.50 – 1.10)	0.74 (0.68 – 3.28)
Double orphan	0.62 (0.31 – 1.21)	0.85 (0.78 – 1.53)	0.66 (0.41 – 1.07)
Duration with HIV	0.92 (0.83 – 1.01)	0.94 (0.88 – 1.02)	0.94 (0.88 – 1.01)
Duration on ART	0.96 (0.87 – 1.06)	0.95 (0.87 – 1.05)	0.98 (0.91 – 1.06)
Depressive symptoms	**0.88 (0.81 – 0.97)***	**0.89 (0.83 – 0.95)***	**0.90 (0.85 – 0.95)***
Adherence self-efficacy	0.99 (0.97 – 1.01)	1.00 (0.99 – 1.01)	0.99 (0.98 – 1.01)
Takes other medications	1.96 (0.77 – 4.97)	1.32 (0.64 – 2.77)	1.50 (0.68 – 3.28)
More than one HIV drug	1.10 (0.74 – 1.64)	1.09 (0.78 – 1.53)	1.07 (0.80 – 1.42)
Substance use	1.40 (0.37 – 5.26)	1.36 (0.44 – 4.17)	1.04 (0.34 – 3.14)
Random effects			
Clinic intercept variance	0.10 (0.01 – 7.74)	<0.01 (<0.01 - <0.01)	<0.01 (<0.01 - <0.01)
Child intercept variance	2.43 (0.36 – 16.31)	<0.01 (<0.01 - <0.01)	<0.01 (<0.01 - <0.01)

***** *Statistically significant associations***.** *OR = Odds Ratio; CI = Confidence Interval*

Sensitivity analysis.

Two sensitivity analyses were conducted. ***First***, a comparison of baseline characteristics between participants with complete data (included in the primary analysis) and those with missing data was conducted to determine any bias due to excluding participants with missing data (**Supplementary Table 1)**. No significant differences were observed across the two groups.

Secondly, complete data was generated through multiple imputations using chained equations. Multilevel logistic regression analysis was then conducted, using the multiply imputed data, following the same steps used in the regression models based on complete case

analysis (presented above). Analysis from the imputed data indicated that none of the three adherence methods significantly predicted viral suppression (Refer to **Supplementary Table 2**).

Aim 2: To develop and validate a model to predict the risk of virological failure.

This section presents results on developing and validating a model to predict virologic failure among ALHIV, based on the hypothesis that the model would achieve a predictive performance with an AUC of at least 0.8. This selection of predictors was informed by insights from the Asset theory (Sherraden, 1990), HBM (Hochbaum, 1958), socioecological model (Bronfenbrenner, 1979), and findings from a risk prediction model for ART adherence among ALHIV in Uganda (Brathwaite et al., 2021).

Detailed information about the distribution of the predictors used in developing the risk prediction models is provided in **Table 1.** Among the 530 participants with complete data (used in the primary analysis for the current aim), 168 ALHIV experienced virologic failure—defined as having >200 copies/ml (Ministry of Health, 2022)—which represented a virologic failure level of 31.7%.

Predictors retained in the final model.

In total, 37 candidate predictor variables were initially identified for inclusion in developing the model. However, after performing the Lasso logistic regression model with 10-fold cross-validation, only **24 predictors were retained based on a selected lambda value of 0.0071304**. **Table 6** shows the predictors that were retained in the final model.

At the ***individual level***, the factors that were retained in the predictive model included the participant's age, sex, employment status (whether the adolescent was working for pay), HIV-related stigma, depressive symptoms, adherence self-efficacy, and HIV clinical knowledge. Additionally, interaction terms for the duration of ART and ART adherence were included in the model.

Table 6: Lasso regression for the predictors of virologic failure among 530 ALHIV.

Predictor variable	Penalized coefficients
Individual level	
Participant age	0.132677
Sex assigned at birth	-0.382465
The participant is in school	x
Adolescent works for pay	-1.340594
HIV stigma*	1.912794
Depressive symptoms*	0.501684
Hopelessness	x
Self-concept	x
Adherence self-efficacy	0.013665
Quality of life	x
Personal health	x
HIV/AIDS clinical knowledge (min/max: 0 to 9)	
Spline 1 (0 to 3)	x
Spline 2 (4 to 6)	-0.144881
Spline 3 (7 to 9)	0.586450
Duration (years) with HIV*	x
Duration (years) on ART	
Below five years	x
Five to nine years	x
Ten to 16 years	x
Less than five years on ART# poor ART adherence	-0.381809
Less than five years on ART# good ART adherence	x
Five to nine years on ART# poor ART adherence	-0.252882
Five to nine years on ART# good ART adherence	0.520512
Ten to 16 years on ART# poor ART adherence	0.411928
Ten to 16 years on ART# good ART adherence	-0.820492
Duration with HIV # poor ART adherence	0.330762
Duration with HIV # good ART adherence	x
Interpersonal level	
Communication with the caregiver about HIV/AIDS	0.787423
Family cohesion (min/max: 12 to 40)	
Spline 1 (12 to 24)	-0.167856
Spline 2 (25 to 34)	0.050527
Spline 3 (35 to 40)	x
Social support*	-0.017934
The participant is an orphan	0.210544
Number of people living in the household	-0.031005
Community level	
Disclosure of HIV status	x
Years spent at current residence (min/max: 0 to 16)	
Spline 1 (0 to 3)	-0.039938
Spline 2 (4 to 9)	0.106529
Spline 3 (10 to 13)	-0.292778
Spline 4 (14 to 16)	x
Structural level	
Household asset ownership	-0.000803

*Note: *Depressive symptoms and duration with HIV were log-transformed; HIV stigma was inverse-transformed; Social support was transformed using square roots.*

On the other hand, predictors including orphanhood status, household size (the number of people living in the household), communication between the adolescent and the caregiver about HIV/AIDS, family cohesion, and social support were retained in the final model at the ***interpersonal level***.

At the ***community level***, the duration of residence at the current location was the only predictor retained in the final prediction model. Meanwhile, household asset ownership was the only predictor retained in the model at the structural level.

Contribution of the predictors to virologic failure

Given the potential bias in coefficients obtained from Lasso regression, a cross-fit partialing out logistic regression model was fitted to obtain more accurate estimates (see page 45), which were used to calculate the individualized risk for virologic failure **(Table 7)**.

To demonstrate the application of the results presented in **Table 7**, the model was used to calculate the risk for virologic failure for a hypothetical adolescent with the following characteristics. Aged 17 years, female, employed, has HIV stigma score of 30, depressive score of 7, adherence self-efficacy score of 95, HIV clinical knowledge of 7, has had HIV for five years, was on ART for five years, has poor ART adherence, never talks with the caregiver about HIV, family cohesion score of 23, social support score of 98, non-orphaned, residing in a household with 13 members, has lived in the current residence for the last eight years, and has asset ownership of 4 items. The risk score for this participant is calculated in the equation below.

$$\mathbf{Risk} = \mathbf{1}/(\mathbf{1} + \mathbf{exp}(-(\mathbf{0.013} * \mathbf{Age} - \mathbf{0.877} * \mathbf{Sex} - \mathbf{1.733} * \mathbf{Employed} + \cdots - \mathbf{0.027} * \mathbf{Assets}))$$

The risk for virological failure for this participant, derived from the model, is 36.98%.

Table 7: Cross-fit partialing out model for the predictors of virologic failure among 530 ALHIV.

Predictor variable	coefficients
Individual level	
Participant age	0.130
Sex assigned at birth	-0.877
Adolescent works for pay	-1.733
HIV stigma*	8.098
Depressive symptoms*	0.932
Adherence self-efficacy	0.025
HIV/AIDS clinical knowledge (min/max: 0 to 9)	
Spline 2 (4 to 6)	-0.513
Spline 3 (7 to 9)	0.733
Duration (years on ART	
Five to nine years	-0.619
Ten to 16 years	0.242
Less than five years on ART# good ART adherence	1.092
Five to nine years on ART# good ART adherence	3.510
Ten to 16 years on ART# good ART adherence	1.115
Duration with HIV # poor ART adherence	0.984
Duration with HIV # good ART adherence	0.377
Interpersonal level	
Communication with the caregiver about HIV/AIDS	0.575
Family cohesion (min/max: 12 to 40)	
Spline 1 (12 to 24)	-0.334
Spline 2 (25 to 34)	0.173
Social support*	0.109
The participant is an orphan	0.196
Number of people living in the household	0.016
Community level	
Years spent at current residence (min/max: 0 to 16)	
Spline 1 (0 to 3)	-0.224
Spline 2 (4 to 9)	0.216
Spline 3 (10 to 13)	0.073
Structural level	
Household asset ownership	-0.027

*Note: *Depressive symptoms and duration with HIV were log-transformed; HIV stigma was inverse-transformed; Social support was transformed using square roots.*

Model Discrimination

The **final risk prediction model demonstrated strong discriminative power** to distinguish ALHIV with or without virologic failure, evidenced by an AUC of 73.8 (95% CI: 68.3 – 78.0). Refer to **Figure 7**.

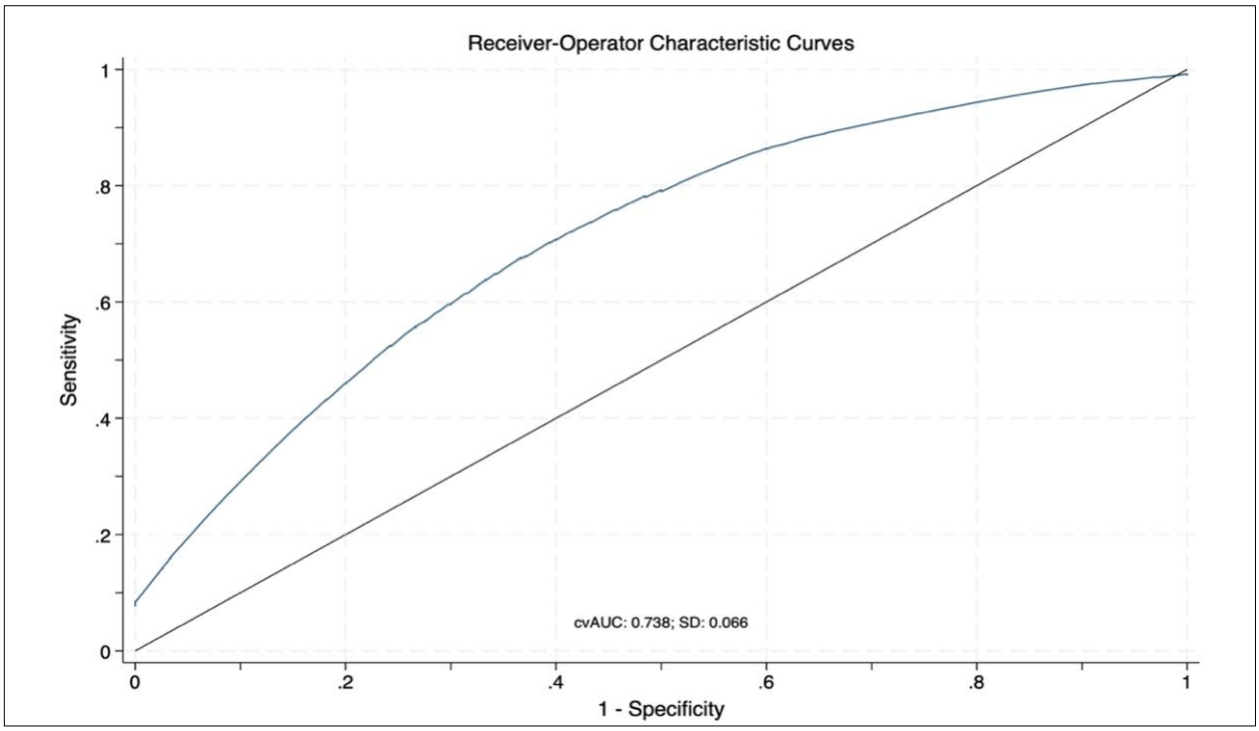

Figure 7: ROC for a model predicting the risk of virologic failure.

Model calibration.

The **model exhibited excellent calibration**, indicating a high level of agreement between the observed and the predicted risks for virologic failure, as illustrated in **Figure 8**. Notably, the calibration slope for the final model, following bootstrap optimism correction, was 0.985, which was close to 1 (perfect calibration).

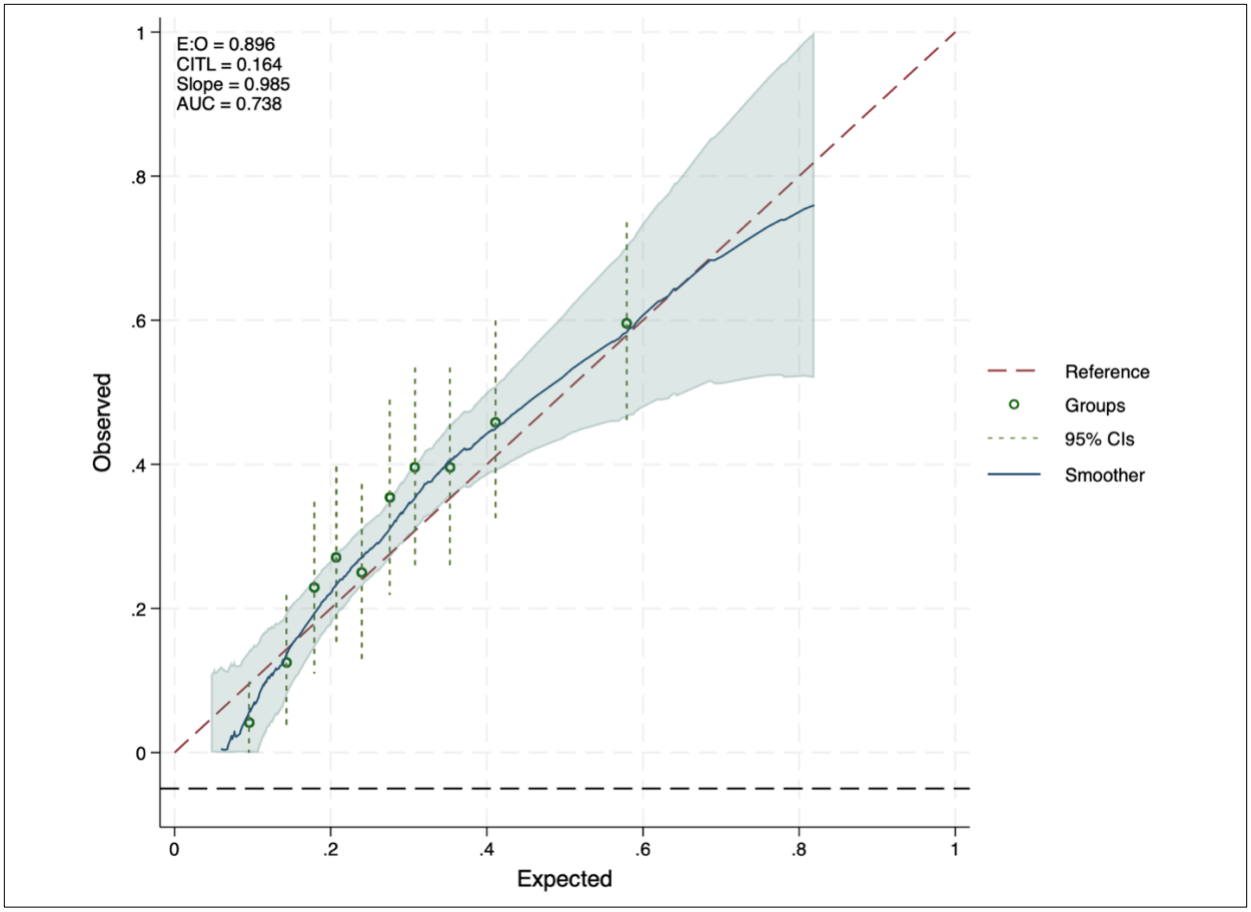

Figure 8: A calibration plot for the performance of the risk prediction model for virologic failure.

The calibration plot was generated using the 'pmcalplot' package in Stata. The expected risk was partitioned into deciles, and the observed virologic failure rates were plotted against these deciles, with a smoother added (blue line). The green circles, and the dotted vertical lines on either side denote the mean predicted risks for virologic failure and their corresponding 95% confidence intervals. The reference line is represented by a red straight dotted line, serving as a point of comparison to assess the alignment between predicted and observed virologic failure rates.

Further analysis using the *calibrationbelt* package in Stata showed no miscalibration regions on the calibration plot, as evidenced by a non-significant test statistic value of 2.86, p-

value = 0.091. This observation further supports the conclusion of excellent model calibration. Throughout the plot, the perfect-fit (reference) line consistently fell within the calibration band (lime green region), indicating that all the predicted risks of virologic failure agreed with the observed virologic failure.

Sensitivity analysis

Since the analysis was conducted after excluding participants with incomplete data, the participants' sociodemographic characteristics were compared to those excluded. **Supplementary Table 3** compares these characteristics, revealing mostly comparable attributes between the two groups. However, notable differences in age, sex, education (whether the participant was enrolled in school), employment status (whether the participant worked for pay), depressive symptom scores, and orphanhood status were observed.

Therefore, multiple imputation was performed to ensure the robustness of the results, generating five complete datasets. Separate datasets were extracted using the *mi extract* command in Stata, followed by applying a Lasso model to each dataset to determine the variables selected. The same set of variables—similar to those in the complete case analysis—were consistently retained in the models derived from each multiply imputed dataset. The variables selected for each dataset are shown in **Supplementary Table 4**.

Aim 3: Mediators of the effect of an EE intervention on ART adherence.

This aim builds on the Asset theory (Sherraden, 1990) and the HBM (Hochbaum, 1958) to examine the direct and indirect pathways through which the economic strengthening intervention impacts ART adherence among ALHIV. **Table 8** summarizes the distribution of the mediating factors and the adherence levels (outcome).

Table 8: Distribution of ART adherence and its mediators with the intervention.

Characteristics	Mean (SD)/ number (Percentage)		
	Control	**Intervention**	**Total**
Items for ART adherence (at year seven)			
Last time you missed HIV medication.			
Less than four weeks."	85 (24.7)	44 (21.9)	129 (23.7)
More than one month	259 (75.3)	157 (78.1)	416 (76.3)
Days you missed medicine (min/max: 0 to 30)*	0.63 (1.90)	0.42 (0.84)	0.55 (1.60)
Did a good job taking your HIV medicine*			
"Very Poor" to "Fair"	40 (11.6)	14 (6.97)	54 (9.91)
"Good" to "excellent"	304 (88.3)	187 (93.0)	491 (90.1)
Took HIV medicine as recommended*			
"Never" to "Sometimes"	40 (11.6)	22 (10.95)	62 (11.4)
"Usually" to "Always"	304 (88.3)	179 (89.1)	483 (88.6)
How hard was it for you to take HIV medicine			
"Extremely Hard" to "Somewhat Hard"	37 (10.8)	20 (9.95)	57 (10.5)
"Not Very Hard" to "Not Hard at All"	307 (89.2)	181 (90.1)	488 (89.5)
Mediators (at year six)			
Adherence self-efficacy (min/max: 20 to 120)	98.0 (19.8)	96.7 (18.7)	97.5 (19.3)
Barriers to medical care (min/max: 0 to 8)	1.49 (1.91)	1.47 (1.75)	1.48 (1.84)
Care transition readiness (min/max: 33 - 85)	74.0 (7.44)	73.7 (8.67)	73.9 (7.95)
Current residence (residence transition)			
Own residence/partner	107 (31.1)	54 (23.7)	161 (28.2)
Parent/other relative	211 (61.3)	155 (68.0)	366 (64.0)
Other residences$^{\phi}$	26 (7.56)	19 (8.33)	45 (7.87)
Employment status (Work transition)			
Currently employed	154 (44.8)	102 (44.7)	256 (44.8)
Not employed but was employed	67 (19.5)	37 (16.2)	104 (18.2)
Never employed	123 (35.8)	89 (39.0)	212 (37.1)

**These questions are from Wilson's three-item scale and were specific to the last 30 days; ϕOther residences include the boss' house, school quarters, and workplace. SD, Standard deviation.*

On average, the participants missed their medication once in the past 30 days. Most participants reported managing their medication intake very well, with 88.6% (n=483 ALHIV), taking their medication as recommended by the health worker. Regarding employment status, nearly half of the participants, 44.8% (256 ALHIV), were employed, 104 ALHIV (18.2%) had been previously employed but were unemployed at the time of the interview, while the rest had never been employed. Additionally, 28.2% (161 ALHIV) reported living in their own or their spouse's residence.

Direct and Indirect intervention effects

The analysis tested two hypotheses as elaborated in the introduction. **H3a** proposed that participants in the intervention group would exhibit higher mean ART adherence levels than those in the control group. Hypothesis **H3b** posited that the effect of the intervention on ART adherence would be mediated by *adolescent social transition, barriers to medical care*, and *adherence self-efficacy*.

Table 9: Model fit indices for the measurement and structural models.

Model	RMSEA	CFI	SRMR	$\chi 2$	df	P value
Measurement Models						
ART adherence	0.059 (0.033, 0.086)	0.996	0.031	4020.4	15	<0.001
Adolescent social transition	0.033 (<0.001, 0.096)	0.996	0.013	356.43	6	<0.001
Barriers to medical care	0.031 (0.008, 0.050)	0.989	0.061	1305.0	36	<0.001
Adherence self-efficacy	<0.001 (<0.001, <0.001)	1.000	<0.001	273.38	3	<0.001
Structural Model						
Final structural model	0.019 (0.011, 0.025)	0.951	0.143	1737.2	378	<0.001

ART, Antiretroviral therapy; CFI, Comparative fit index; RMSEA, Root Mean Square Error of Approximation SRMR, Standardized Root Mean Square Residuals

As shown in **Table 9** above, the measurement and structural models achieved good fit. Specifically, all models reported RMSEA values below 0.06. Furthermore, each model achieved a CFI of at least 0.95 and SRMR of less than 0.08, except for the structural model, which, although slightly lower, still demonstrated an excellent overall fit (Hu & Bentler, 1999). Results from the sequential longitudinal mediation models are presented in **Table 10** and **Figure 9**.

Table 10: Mediators of the effect of the intervention on ART adherence.

Associations	β (95% CI)	p-value
Intervention → mediators		
Adolescent social transition	0.044 (-0.038, 0.126)	0.295
Barriers to medical care	**-0.178 (-0.259, -0.096)**	**<0.001**
Adherence self-efficacy	0.001 (-0.062, 0.065)	0.969
Mediators → ART adherence		
Adolescent social transition	0.042 (-0.064, 0.149)	0.437
Barriers to medical care	**0.170 (0.036, 0.304)**	**0.013**
Adherence self-efficacy	**0.144 (0.070, 0.218)**	**<0.001**
Specific indirect effects		
Adolescent social transition	0.002 (-0.003, 0.007)	0.448
Barriers to medical care	**-0.030 (-0.057, -0.004)**	**0.026**
Adherence self-efficacy	0.001 (-0.009, 0.009)	0.969
Effects from the intervention to ART adherence		
Direct effect (Intervention → ART adherence)	**0.066 (0.007, 0.125)**	**0.028**
Total indirect effect	**-0.028 (-0.054, -0.002)**	**0.033**
Total effect	0.038 (-0.021, 0.097)	0.207

ART, Antiretroviral therapy; CI, Confidence Interval

On examining the pathways between the intervention and ART adherence, a **significant direct effect of the intervention on ART adherence** was observed**,** β = 0.066 (0.007, 0.125), p =

0.028. In other words, ALHIV who participated in the EE intervention had higher ART adherence levels compared to those in the control group. This result supports hypothesis **H3a**. Furthermore, the analysis identified a **significant total indirect effect of the intervention on ART adherence,** β = -0.028 (-0.054, -0.002), p = 0.033, as was hypothesized in H3b.

The indirect effect of the intervention on ART adherence was mediated through barriers to medical care, β = -0.030 (-0.057, -0.004), p = 0.026. Specifically, the intervention was efficacious in reducing the barriers to medical care, β = -0.178 (-0.259, -0.096), p < 0.001. However, paradoxically, participants experiencing more barriers to medical care also reported higher levels of ART adherence, β = 0.170 (0.036, 0.304), p = 0.013.

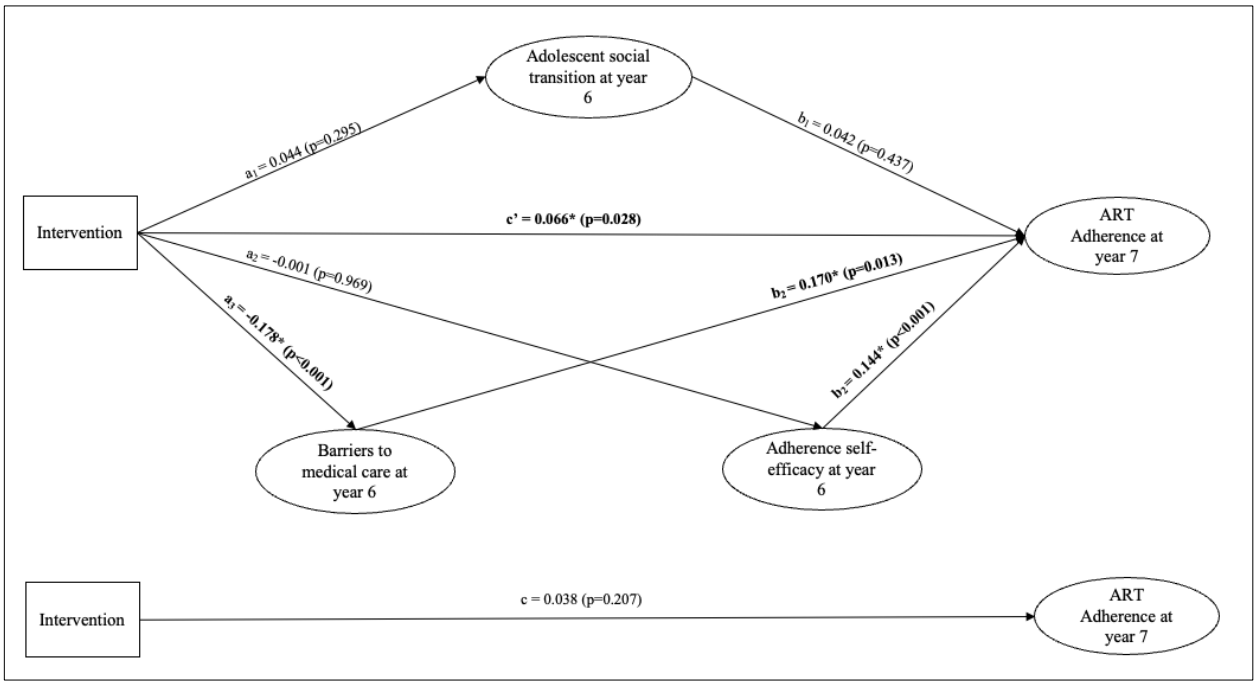

Figure 9: A SEM for the mediators of the effect of an EE intervention on ART adherence.

Note: Standardized coefficients are presented, and significant associations are represented by an asterisk.

Sensitivity analysis

Including the participant's age, sex, and orphanhood status in the model to assess their potential impact on the observed relationships did not yield significant changes to the model results and were not included in the final model.

Chapter 6: Discussion

Poor ART adherence is a significant barrier to viral suppression and overall HIV control, making it critical to monitor ART adherence accurately. This dissertation addressed three research aims. *First*, it compared the performance of three adherence measures —self-reports, pill counts, and electronic adherence using Wisepill devices—in monitoring ART adherence and predicting viral suppression. *Secondly*, it developed a model to predict the risk of virologic failures, and *finally*, it examined the pathways through which an economic empowerment intervention influences ART adherence among ALHIV in Uganda. In the next sections, this chapter puts into perspective the results, organized according to the dissertation aims.

Performance of the measures of ART Adherence.

The analysis for the **first aim** of this dissertation had three main findings. ***First***, a notable proportion of the participants had poor ART adherence and low levels of viral suppression, with nearly one-quarter failing to meet the recommended thresholds for good adherence (Ministry of Health, 2022) and approximately 33% unable to achieve viral suppression. The low ART adherence reported in this dissertation aligns with results from other studies. For instance, a study conducted among ALHIV in Ethiopia found that 20.9% of the participants had poor **self-reported adherence** (Firdu et al., 2017), while another study in Malawi among 519 ALHIV revealed that 45% of the participants reported poor adherence (Kim et al., 2017). More recent studies from other African countries have shown similar results (Brittain et al., 2018; Zhou et al., 2021). While studies reporting **pill count** ART adherence remain scarce, a recent study from Tanzania reported pill count adherence of only 62.5% (Martelli et al., 2019), while systematic reviews among ALHIV found comparable adherence of 65% (Hlophe et al., 2023; Kamau et al., 2024). Concurrently, recent studies examining **viral suppression** among ALHIV in SSA have

found low viral suppression levels. A study in South Africa reported that 19% and 30% of the young and older ALHIV, respectively, experienced virologic failure (Brittain et al., 2018), while the study by Martelli in Tanzania reported virologic failure rates reaching 35% (Martelli et al., 2019). The observed suboptimal adherence and low viral suppression rates represent significant public health concerns, as poor adherence increases the risk of viral failure for ALHIV. In contrast, elevated viral loads pose an increased risk for HIV transmission, thereby undermining HIV control efforts.

***Secondly*,** comparing the adherence measures revealed a **discordance among the three methods, particularly evident when the adherence levels were low**. However, as adherence levels increased, the disagreement between measures diminished such that at the adherence of 90%, there was barely any bias across any given pair of adherence measures. The observation of diminishing bias with increasing adherence is reassuring, considering that the majority (~75%) of participants achieved good adherence. In other words, for the participants with good ART adherence, similar ART adherence would be irrespective of the adherence measure used. In resource-constrained settings, these results underscore the utility of cost-effective adherence measures such as self-reports, yielding comparable results to the logistically demanding electronic adherence measures. However, the results also suggest an increased likelihood of inaccurately measuring ART adherence in ALHIV with low mean ART adherence—which carries important clinical and public health ramifications regarding treatment outcomes and HIV control.

Various explanations have been suggested for the disagreement between subjective and objective adherence measures, mainly centered around the weaknesses associated with each adherence measure. For instance, Lowenthal and colleagues conducted a qualitative study on

adolescents in Botswana, revealing themes such as pill manipulation to deceive clinicians during pill counts and dishonest reporting of adherence, driven by fears of judgment from healthcare providers and caregivers, aversion to intensified adherence counseling, and feelings of guilt associated with missed medication (Lowenthal et al., 2022). Furthermore, the pill count method yields inaccurate adherence estimates if patients share pills. Another shortcoming of pill counts is that the patients can manipulate the method by discarding some pills—also called "pill dumping"— hence over-estimating adherence. (Biressaw et al., 2013). Similarly, Wisepill suffers some limitations when measuring adherence. For instance, studies have quoted adolescents who reported not using the device because it is bulky to carry around, associated with stigma, or were afraid of it being stolen or misplaced (MacCarthy et al., 2020). Instead, they kept their pills in a separate container but did not interrupt their adherence routines. In such circumstances, although the device did not register an ingested pill—since it was not used—the patients continued adhering to the treatment—resulting in underestimation of ART adherence. However, no such incidences were encountered in the current study.

***Third*,** after adjusting for covariates, **only self-reported adherence was significantly associated with viral suppression**, providing further evidence for the relevance of self-report in monitoring treatment in ALHIV. These findings align with those reported by Brittain among ALHIV in South Africa, who identified a significant association between the 30-day recall self-reported adherence and viral suppression (Brittain et al., 2018). Similar results have been reported in Zimbabwe (Chikwari et al., 2017). In contrast, objective adherence measures including pill counts and electronic methods—which are considered superior to self-reported adherence—demonstrated poor performance in predicting viral suppression. Martelli and colleagues found similar results when pill count adherence was used to predict virologic failure

among ALHIV in Tanzania (Martelli et al., 2019). However, some previous studies have shown that objective adherence measures outperformed self-reports in predicting viral suppression (Orrell et al., 2017; Sangeda et al., 2014). The mixed results on the performance of the various adherence measures in predicting viral suppression call for more research to streamline their performance, but also develop more reliable adherence and affordable measures, especially for ALHIV in resource limited settings.

The superior performance of self-reported adherence observed in this study may be attributed to several factors. One plausible explanation is that unlike most other studies that rely on a single item to assess self-reported adherence, this dissertation employed three questions, as Wilson proposed (Wilson et al., 2016). These three items are less susceptible to recall and social desirability biases. Another possible reason for the superior performance of the self-report measure is that our study team has established trust with the participants, having worked in this community for over two decades. This trust could mitigate participants' bias in reporting adherence.

Another finding from this analysis was that all the measures predicted viral suppression with sensitivity above 75%, specificity below 30%, and AUC slightly above 0.6, consistent with earlier studies assessing the prediction of viral suppression using adherence measures. For instance, a recent systematic review by Smith and colleagues showed high sensitivity and low specificity of adherence measures in predicting viral suppression (Smith et al., 2022). Also, Zhou and colleagues found, in their study among ALHIV in South Africa, high sensitivity (>90%), low specificity (<30%), and an AUC of 0.64 for self-reported adherence in predicting viral suppression (Zhou et al., 2023). While the sensitivity reported in their study was higher than that observed in the present dissertation study, it is essential to note that their study defined *virologic*

failure as having >1000 copies/mL, and self-reported adherence was assessed using a 3-day missed pill recall. Overall, the notably high sensitivity observed in the current study indicates that achieving viral suppression was associated mainly with attaining good ART adherence, regardless of the specific adherence measure utilized. In other words, all the adherence measures effectively identified virally suppressed ALHIV with considerable certainty. However, the low specificity suggests that the adherence measures had limited discriminatory ability in predicting ALHIV with virologic failure. In other words, several participants with virologic failure also demonstrated good ART adherence. These results imply that factors beyond ART adherence such as drug resistance, ART pharmacokinetics, and clinical and psychosocial factors, which were not measured in this study (Pham, 2009), could also be responsible for influence viral suppression.

Taken together, these findings suggest that **health workers in clinical settings and researchers may continue to use self-reported adherence** since it can potentially flag ALHIV virologic failure; this is particularly crucial given affordability of the self-reported adherence and the challenges with viral load testing including the infrequent nature of viral load testing, the time required for test results to be returned, and the financial burdens associated with such testing. Self-report enables a rapid initial assessment of the risk of virologic failure, even in busy LMIC HIV clinics, and allows for immediate feedback and further intervention. However, it is essential to recognize that more than adherence alone may be needed to capture all the factors influencing viral suppression fully. Therefore, there is a need for more accurate predictive tools that can better streamline adherence monitoring and its impact on viral outcomes.

Developing a model to predict the risk of virological failure.

Given that HIV is not yet curable, achieving viral suppression is among the final goals in the HIV care continuum. However, even with the availability of ART, many ALHIV fail to achieve virologic failure, which calls for more efforts to increase virologic suppression. Several studies have examined the factors driving virologic failure in this group. However, a gap exists in utilizing this knowledge, with the scarcity of studies developing tools, based on the known risk factors, that can be used to identify ALHIV at increased risk for virologic failure. Dissertation **aim 2** developed and tested a model to predict virologic failure among ALHIV in a low-resourced setting. The results showed that it is possible to accurately predict virologic failure using sociodemographic, psychological, and economic characteristics.

The risk prediction model included information that was obtained from the participants solely through interviews, without the need for any invasive procedures. The information included the participants' age, sex, work status, stigma, depressive symptoms, adherence self-efficacy, HIV knowledge, duration with HIV, and time spent on ART, communication with the caregiver, family cohesion, social support, orphanhood status, number of people in the household, HIV disclosure, years spent at the current residence, and household asset ownership. Available literature has already demonstrated that most of these variables are known risk factors for virologic failure. For example, in their risk prediction model for viral suppression in adults, Gebrezgi and colleagues found the participants' age and poverty levels among the factors predicting virologic failure (Gebrezgi et al., 2020). The same factors have been demonstrated to predict other outcomes among ALHIV. For example, Rachel Brathwaite and colleagues found that adherence self-efficacy, family cohesion, and poverty were among the factors that predicted poor ART adherence in ALHIV (Brathwaite et al., 2021).

The overall performance of the prediction model was good, with a c-statistic of 0.734, which was slightly higher than the 0.699 reported by Brathwaite and colleagues (Brathwaite et al., 2021). Similarly, an almost perfect calibration, approximately equal to 1, was observed. Given the scanty risk prediction models for virologic failure in ALHIV, the current model could only be compared to those developed to predict virologic failure in adults. Nonetheless, the current model performed well when compared to these models. For instance, in their model predicting virologic failure among adults with HIV in the USA, Gebrezgi and colleagues found a c-statistic of 0.763, which was included within the confidence interval of the current model—suggesting comparable performance. It is worth noting that in their model, they used a different set of predictors and had a large sample size of 6492 participants. Contrastingly, other studies among adults with HIV have reported higher performance, with a C-statistic of ~0.8 (Powers et al., 2018; Robbins et al., 2010). However, clinical characteristics such as the CD4 count, which are significant predictors of virologic failure, were included among the predictors in these models—unlike the current model.

The current model builds on Brathwaite's model (Brathwaite et al., 2021), by making the following advancements, which could explain the superior performance—the excellent calibration and discriminative ability—of the current model. **1)** The outcome for the current model is virologic failure—instead of ART adherence—which is the end goal for HIV care and carries critical public health implications regarding the increased risk of HIV spread. Moreover, the model applied the recently updated definition of virologic failure of having >200 copies/ml (Ministry of Health, 2022); **2)** More predictors were incorporated in the current model, such as the duration on ART, and the duration that the participant has lived at the current address; **3)** The intervention has been excluded in the current as one of the predictors by utilizing only baseline

data. Exclusion of the intervention makes the model more applicable to external datasets since data on the intervention is expensive to collect and is not readily available outside the highly controlled research setting, and **4)** More rigorous data preparation has been employed including linearization of variables and adding interaction terms to the models (see data analysis section).

Other possible explanations for the superior performance of this model may include the careful selection of predictors used in the model, being informed by three complimentary theories including the socioecological model (Bronfenbrenner, 1979), health belief model (Hochbaum et al., 1952), and the asset theory (Sherraden, 1990), but also building on available literature of the predictors for virologic failure; and the addition of interaction terms to the model, which provided more accuracy on how the variables interact to influence viral suppression. Additional strengths of the current model lie in the use of a large sample size to develop the model, employing robust methods such as the LASSO regression model— which is recommended as compared to backward and other selection models used in many previous models— in selecting the predictors to include in the final model, utilizing standardized scales to collect the information on the predictors, using an objective biomarker (viral load) as the outcome.

In summary, the second aim of this dissertation demonstrated the utility of a model developed using sociodemographic, psychological, behavioral, and economic factors in predicting the risk of virologic failure among ALHIV. The model showed good performance and promise for adding value in the care for ALHIV. However, there is still need for more research in improving the discriminatory power of the model, which could be achieved by including more risk factors for viral suppression such as the CD4 count and HIV clinical stage. Future research

can build on the current model to make it more parsimonious by using fewer and simpler measures for the variables used in the model.

Mediators of the effect of an EE intervention on ART adherence.

The dissertation's third aim sought to understand better the potential mediators of the effect of an EE intervention on ART adherence. The study examined whether participating in an EE intervention resulted in better ART adherence among ALHIV and whether this relationship was mediated by adolescent social transition, barriers to medical care, and adherence self-efficacy. The results make significant contributions by showing that the EE intervention significantly improves ART adherence seven years later and that barriers to medical care and adherence self-efficacy mediated this effect. Below is a detailed discussion of these findings.

Direct intervention effects.

The positive effect of the intervention on ART adherence supports the Asset theory—which proposes that the accumulation of assets has non-economic benefits such as psychological, behavioral, and health outcomes (Sherraden, 1990). The impact of EE interventions on health-related outcomes among ALHIV is well documented in other studies. For example, our team recently published an article demonstrating the positive effect of economic empowerment interventions on ART adherence (Kizito et al., 2024). Also, Ssewamala and colleagues used data from the *Suubi+Adherence study* (the same data source for the current dissertation study) to demonstrate the positive impact of the EE intervention on viral suppression among ALHIV (Bermudez et al., 2018; Ssewamala et al., 2020). Similar results have been reported for other outcomes, including improved academic performance (Kizito, Nabayinda, Kiyingi, et al., 2023),

mental health functioning (P. Cavazos-Rehg, W. Byansi, C. Xu, et al., 2021), and sexual risk-taking behaviors (Ssewamala et al., 2023).

The positive effect of the intervention on ART adherence and other outcomes could be explained using the tenets put forward in the Asset theory. To illustrate, by providing the ALHIV and their families with financial resources, they were able to meet the indirect costs associated with medical care such as transportation costs for clinic appointments, thus overcoming the barriers to medical care—resulting in sustained optimal ART adherence.

Indirect intervention effects.

The results provided evidence for the mediating effect of barriers to medical care on the influence of the EE intervention on ART adherence. Previous studies from our team at ICHAD have examined the potential mediating effects of factors such as mental health outcomes, HIV stigma, family cohesion, and food security on the influence of the EE intervention on ART adherence (Patricia Cavazos-Rehg et al., 2021; Kizito, Nabayinda, Neilands, et al., 2023). The current study builds on this prior research by being the first study to provide robust empirical evidence of the mediating effect of barriers to medical care as a specific pathway through which economic interventions enhance ART adherence, among ALHIV in SSA. An interesting finding of this study was that the indirect effect of the intervention on ART adherence through barriers to medical care dampened ART adherence. A closer examination of this specific pathway reveals potential explanations for this surprising trend. Specifically, although the intervention significantly reduced the barriers to medical care, the participants who reported more barriers also reported higher ART adherence and vice versa. Therefore, increased barriers to medical care — which were more reported by participants in the control group — also increased ART adherence, undermining the intervention's effect on ART adherence.

This positive relationship between the barriers to medical care and ART adherence contrasts previous literature, which has demonstrated that barriers to medical care reduce ART adherence (Adams et al., 2022; Cluver et al., 2021; MacCarthy et al., 2016). A possible explanation for the reversed trend is the alternative coping strategies that the ALHIV develop to overcome these barriers, as supported by prior research. For instance, Adams conducted a qualitative study among ALHIV in Kenya and found that resilience was a significant driver behind maintaining good ART adherence (Adams et al., 2022). Other studies have reported similar findings relating resilience to better ART adherence in ALHIV (Harrison & Li, 2018; Woollett et al., 2016). Also, there could be other factors, not assessed in the current model, that could be responsible for the negative mediation through interacting with the barriers to medical care. For example, ALHIV facing more barriers could also have **strong family and social support**, which help them navigate these barriers, while maintaining or even enhancing their adherence. Indeed, in our recent study, we demonstrated that family support had a direct and indirect effect—mediated through adolescent-caregiver communication—on ART adherence (Proscovia Nabunya et al., 2023). In conclusion, the intervention significantly improved ART adherence, and reduced the barriers to medical care, further supporting the arguments put forward by the Asset theory. The results highlight the importance of addressing household poverty as one of the strategies to improve outcomes among ALHIV.

Study limitations.

The following limitations are worth noting when interpreting the results from this dissertation. *First,* the results cannot be generalized to all ALHIV in all settings. Specifically, the data used for this dissertation was from ALHIV in a rural area—Greater Masaka region— with an HIV prevalence of 11.7% which is twice as high as the national prevalence of 5.4%.

Second, relying on predominantly self-reported data, for instance, self-reported adherence, the predictors used in the risk prediction model, (Aim 2), and mediators used in aim 3 present a notable limitation. Self-reported data may be subject to respondent bias, where participants may provide responses, they believe are expected or socially desirable. This can potentially lead to an overestimation of ART adherence and predictors, compromising the accuracy and reliability of the findings. However, due to ICHAD's extensive presence and longstanding relationship with the participants, spanning over a decade of follow-up and more than 20 years of work in the area, the potential for bias in self-reported data may have been minimized.

Specific to dissertation aim 1, the Wisepill devices have limitations when used to monitor ART adherence. The key weakness using EMD is that technical challenges, like signal interruptions and battery failure, cause missing adherence data. In the case of the *Suubi+Adherence* study, however, the field team proactively followed up with participants via phone calls or visits when signals were absent for more than three days, aiming to enhance data accuracy and reduce missing information. In addition, when using EMD for the first time, participants tend, in the early days of receiving the device, to frequently interact with the device, opening it multiple times each day. Consequently, during the initial week, such devices tend to register multiple signals daily. In order to address this possibility – which may impact the reliability of data gathered during the initial usage phase, the data collected within the first week after *Suubi+Adherence* participants received their Wisepill devices was excluded from the analysis. Moreover, beyond this initial period, in cases where participants opened the Wisepill device multiple times for a prescribed dose, the first opening was considered as the moment that the pill was taken and the subsequent signals will be disregarded.

A notable limitation of Aim 2 was the lack of external validation for the risk prediction model for virologic failure. This limitation arose due to the unavailability of an appropriate external dataset that included all variables used in developing the model. Therefore, it is not known how well the current model would perform in different populations and settings. Thus, while the generalizability of our model remains uncertain, its application in identifying ALHIV at increased risk of virologic failure remains promising, particularly in settings similar to the current study location.

In summary, despite the potential limitation highlighted above, the inclusion of both subjective and objective adherence measures in the analysis was a strength allowed this the *Suubi+Adherence* study, and the subsequent analysis included in this dissertation to capture the performance of both the low-cost -- although probably more bias-prone – and the more logistically demanding measures—but less prone to biases.

Chapter 7: Implications for Public Health Practice, Research, and Policy

This dissertation addresses challenges undermining and the strategies to enhance ART adherence and viral suppression among ALHIV in Uganda and similar low-resourced high HIV-burden settings. The findings have several implications for research, practice, and policy since adherence to HIV medication has individual benefits, such as halting the HIV progression to severe disease and low survival rates (Tarantino et al., 2020), as well as public health implications, including reduced HIV spread, and associated healthcare costs (Lowenthal et al., 2014; Mark et al., 2017). The results showed that almost one in four ALHIV failed to achieve optimal ART adherence measured using multiple methods and that one in every three adolescents had low viral suppression levels. Moreover, there was considerable disagreement between the adherence measures, especially when ART adherence is low.

However, despite the sub-optimal ART adherence, low viral suppression, and discordance among the adherence measures, there were also several encouraging results, as well. The self-reported adherence was associated with viral suppression, and a model that can accurately predict the risk of virologic failure among ALHIV was developed using the participant's socioeconomic, behavioral, psychological, and economic information. More importantly, the dissertation showed that providing the ALHIV and their families with financial resources through a combination of economic empowerment intervention positively improved their ART adherence and highlighted alternative pathways influencing this relationship. These findings highlight a pressing need for more efforts to improve ART adherence among ALHIV and the need to incorporate interventions that address poverty in the programs aimed at controlling HIV. An account of the implications of these results is provided below.

Performance of the adherence measures

Adherence monitoring is an essential aspect of routine care for ALHIV. Hence, by understanding the performance of the different adherence measurement methods, clinicians can make informed decisions on how best to monitor ALHIV under their care. However, researchers acknowledge the challenge of accurately measuring ART adherence in HIV-infected adolescents. (Koss et al., 2018; Orrell et al., 2017). This dissertation addressed this challenge by comparing three adherence measures, with important recommendations for clinical practice, research, and policy.

Upon comparing the performance of self-reports, pill counts, and Wisepill adherence measures, the study revealed poor agreement between the three methods, mainly when ART adherence was low but showed considerable agreement at optimal adherence levels. The marked discordance between the adherence measures, especially when the adherence was low, is concerning. This is because ALHIV with poor adherence stand a higher risk for virologic failure, which warrants adherence measures to identify them more accurately. However, the poor agreement among the three measures means that any of the three measures tested in this study could easily miss ALHIV with poor adherence. As such, future research should build on this knowledge to refine adherence assessment tools further.

Moreover, the pill counts and Wisepill, which are considered more objective adherence measures compared to self-reports, showed poor association with viral suppression. Self-reported adherence emerged as a significant predictor of viral suppression. Therefore, any suboptimal self-reported adherence among ALHIV could be clinically relevant and should be further investigated. The superior performance of self-reported adherence is reassuring, given its affordability, logistical feasibility, and widespread use in low-resource settings. Nonetheless, given the variability among adherence measures, caution should be exercised when interpreting

adherence data obtained from any of these adherence measures. Adherence assessments should be complemented with more reliable tests, such as viral load testing—especially for ALHIV reporting low ART adherence—to ensure accurate monitoring of treatment outcomes and inform appropriate clinical decisions. These findings show the necessity for refining existing adherence measures and identifying more objective yet cost-effective alternatives for ALHIV, especially in low-income settings where resources may be limited.

At the policy level, findings from this dissertation provide additional evidence for the relevance of self-reports as a mainstay method for monitoring ART adherence. It also throws more light on whether investing additional resources to implement more sophisticated adherence measures, such as the EMDs is cost-effective. The poor ART adherence and low viral suppression levels found in this study should cause more financial resources to be diverted toward reversing these trends in ALHIV.

Predicting the individualized risk for viral suppression

Developing a risk-prediction model for virological failure in ALHIV was necessary, especially in SSA, where resources are scarce. **Aim 2** of this dissertation developed a model predicting the elevated risk for virologic failure among ALHIV in a low-income setting using socioeconomic, psychological, behavioral, and economic factors. The model used predictor variables that were entirely collected through participant interviews, eliminating the necessity for invasive techniques such as blood draws or collecting other body samples. This approach eliminates the logistical requirements associated with collecting biomarkers for predictors and offers the model more relevance for resource-constrained settings.

From a clinical point of view, this model allows clinicians to identify ALHIV at higher risk of virological failure early enough, enabling the prompt delivery of enhanced and

personalized care. By incorporating this predictive tool into clinical practice, providers can strategically monitor patients more closely and tailor treatment plans— for instance, initiating intensified adherence counseling—to address the specific needs of those at greater risk for virologic failure. This approach empowers healthcare teams to take early, preventive measures to mitigate virological failure risks, ultimately improving the long-term health and well-being of ALHIV.

Researchers could use this model as a foundation for refining future models for better precision and for adapting it to new settings, aiming to identify ALHIV with increased risks for poor outcomes. For instance, there is a need to perform external validation of the current model. In addition, more predictors could be incorporated into the model, especially clinically relevant variables such as the HIV clinical stage and the CD4 count, which could potentially improve the overall discrimination ability of the model. Also, more simpler models utilizing fewer variables and collected using less extensive scales than those used in the current study are recommended to ease the implementation of the model in busy routine care settings in LMICs.

Mediators for the effect of the EE intervention on ART adherence

Given that poverty is a key driver of poor outcomes in ALHIV in LMICs, interventions that enable participants to accumulate financial resources are critical. The results showed that the intervention significantly improved ART adherence – measured by a combination self-reports and pill counts -- through a direct effect. However, the intervention's effect on adherence was also mediated through its effect on addressing the barriers to medical care, which hinder the ALHIV's engagement with the health care system. An interesting finding, however, was that the participants who reported more barriers also had higher ART adherence, suggesting a possibility

of underlying mechanisms such as resilience and social support, which were not studied in the current model. Future research should consider including these factors.

The results also showed that interventions with a financial support component can potentially impact ART adherence by reducing the barriers to medical care. By focusing on mediation analysis, this study expands on our understanding of the complex relationships between interventions addressing poverty and ART adherence, providing further insights into how EE interventions impact health outcomes among ALHIV in low-resourced settings. Future studies should examine the role of factors such as resilience, which could explain the paradoxically enhanced adherence among ALHIV, who experienced more barriers to medical care. These alternative pathways could act as potential targets for future interventions to enhance ART adherence.

Furthermore, understanding these mediation pathways is essential in informing adaptations to make the EE interventions more tailored to the specific needs of adolescents. This information could be used to inform the scalability of this intervention and ensure its effectiveness in the broader population. Recognizing the significance of EE interventions in improving ART adherence among ALHIV, policymakers can consider incorporating poverty alleviation strategies into broader public health policies.

In summary, findings from this dissertation have implications for public health research, practice, and policy on adolescent HIV care. The comparative analysis of adherence measurement methods, the development of a risk prediction model, and the emphasis on EE interventions provided valuable insights into the overall care for ALHIV in resource-limited settings. These findings add to our understanding regarding the need for tailored interventions for ALHIV, data-driven clinical decision-making, and comprehensive care for ALHIV.

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Appendices

Appendix A

Supplementary Table 1: Comparison of ALHIV with and without pill count data.

Characteristics	Complete data n= 455 (%)	Missing data n= 247(%)	P value
Female gender	263 (57.8)	133 (53.9)	0.313
Age in completed years (mean ± SD)	12.6 ± 2.00	12.2 ± 1.93	0.061
Orphanhood status			
Both parents are deceased	120 (26.8)	62 (25.6)	0.824
One parent is deceased	172 (38.4)	90 (37.2)	
Both parents are alive	156 (34.8)	90 (37.2)	
Number of adults in the household	5.8 ± 2.52	5.6 ± 2.63	0.360
Number of children in the household	2.4 ± 1.95	2.2 ± 2.1.87	0.145
ARV treatment regimen			
First line treatment regimen	277 (60.9)	161 (65.2)	0.378
Second line treatment regimen	178 (39.1)	86 (34.8)	
Number of pills taken per day			
Less than 2 pills	285 (62.6)	160 (64.8)	0.287
Two to four pills	97 (21.3)	58 (23.5)	
More than 4 pills	73 (16.0)	29 (11.7)	
Frequency of medication			
Once a day	64 (14.1)	13 (8.8)	0.099
More than once a day	391 (35.9)	134 (91.2)	

APPENDIX B

Supplementary Table 2: MI regression of ART adherence and viral suppression.

	Self-reports β (95% CI)	**Pill count. β (95% CI)**	**Wisepill β (95% CI)**
Adherence measure	0.01 (-0.01, 0.02)	0.01 (-0.02, 0.02)	0.01 (-0.01, 0.01)
Participant age	-0.03 (-0.12, 0.07)	-0.03 (-0.12, 0.07)	-0.03 (-0.12, 0.06)
Female sex	**0.35 (0.01, 0.69)***	**0.35 (0.02, 0.69)***	**0.35 (0.02, 0.69)***
Orphanhood status			
Non-orphan	Ref	Ref	Ref
Single orphan	-0.23 (-0.64, 0.18)	-0.21 (-0.62, 0.19)	-0.22 (-0.62, 0.19)
Double orphan	-0.31 (-0.75, 0.14)	-0.31 (-0.75, 0.14)	-0.30 (-0.75, 0.14)
Duration with HIV	-0.02 (-0.09, 0.05)	-0.03 (-0.10, 0.04)	-0.03 (-0.10, 0.04)
Duration on ART	-0.03 (-0.09, 0.04)	-0.02 (-0.08, 0.04)	-0.02 (-0.08, 0.04)
Depressive symptoms	**-0.07 (-0.12, -0.01)**	**-0.07 (-0.12, -0.02)***	**-0.07 (-0.12, -0.02)***
Self-concept	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)
Adherence self-efficacy	-0.01 (-0.01, 0.01)	-0.01 (-0.01, 0.01)	-0.01 (-0.01, 0.01)
Takes other medications	0.44 (-0.17, 1.05)	0.42 (-0.19, 1.04)	0.42 (-0.19, 1.03)
More than one HIV drugs	0.06 (-0.19, 0.31)	0.07 (-0.18, 0.32)	0.07 (-0.18, 0.32)
Substance use	0.32 (-0.46, 1.10)	0.31 (-0.47, 1.08)	0.29 (-0.48, 1.07)
Random effects			
Clinic intercept log variance	-2.34 (-4.18, -0.52)	-2.30 (-4.07, -0.52)	-2.34 (-4.18, -0.51)
SD of clinic effects	0.31 (0.12, 0.77)	0.32 (0.13, 0.77)	0.31 (0.12, 0.77)
ICC	0.028 (0.005, 0.153)	0.030 (0.005, 0.153)	0.028 (0.005, 0.154)

***** *Statistically significant associations*

APPENDIX C

Supplementary Table 3: Comparing ALHIV with and without missing data.

Predictor variable	Complete (n=530)	Missing (n=172)	P value
Individual level			
Participant age (min/max: 10 to 16)	12.2 (1.83)	13.2 (2.19)	<0.001*
Sex assigned at birth (Female)	313 (59.1)	83 (48.3)	0.022
The participant is in school	530 (100)	83 (48.3)	<0.001
Adolescent works for pay	39 (7.39)	26 (15.1)	0.003*
HIV stigma (min/max: 9 to 35)	18.2 (5.77)	19.2 (6.37)	0.166
Depressive symptoms (min/max: 0 to 20)	5.0 (3.73)	5.9 (3.83)	0.023*
Adherence to self-efficacy (min/max: 20 to 120)	94.9 (0.99)	92.3 (24.2)	0.343
Quality of life (min/max: 4 to 20)	14.1 (0.16)	14.9 (0.26)	0.067
Good personal health	402 (75.9)	125 (72.7)	0.431
HIV/AIDS clinical knowledge (min/max: 0 to 9)	5.9 (1.99)	6.2 (1.94)	0.167
Duration (years) with HIV (min/max: 0 to 16)	3.61 (3.01)	3.74 (3.16)	0.589
Duration (years) on ART (min/max: 0 to 16)	4.0 (3.39)	3.17 (3.26)	0.373
Good ART adherence	276 (52.1)	99 (57.9)	0.540
Interpersonal level			
Communication with caregiver about HIV/AIDS	277 (52.3)	86 (50.0)	0.424
Family cohesion (min/max: 12 to 40)	31.9 (6.82)	31.3 (6.448)	0.250
Social support (min/max: 56 to 120)	88.8 (14.07)	86.0 (14.01)	0.122
The participant is an orphan	334 (63.0)	110 (68.8)	0.006*
People living in the household (min/max: 2 to 18)	5.72 (2.40)	5.82 (2.98)	0.600
Community level			
Disclosure of HIV status	7.5 (3.19)	7.3 (3.02)	0.637
Years spent at current residence (min/max: 0 to 16)	8.58 (4.44)	8.36 (4.84)	0.651
Structural level			
Household asset ownership (min/max: 1 to 20)	11.0 (3.44)	10.1 (3.76)	0.003*

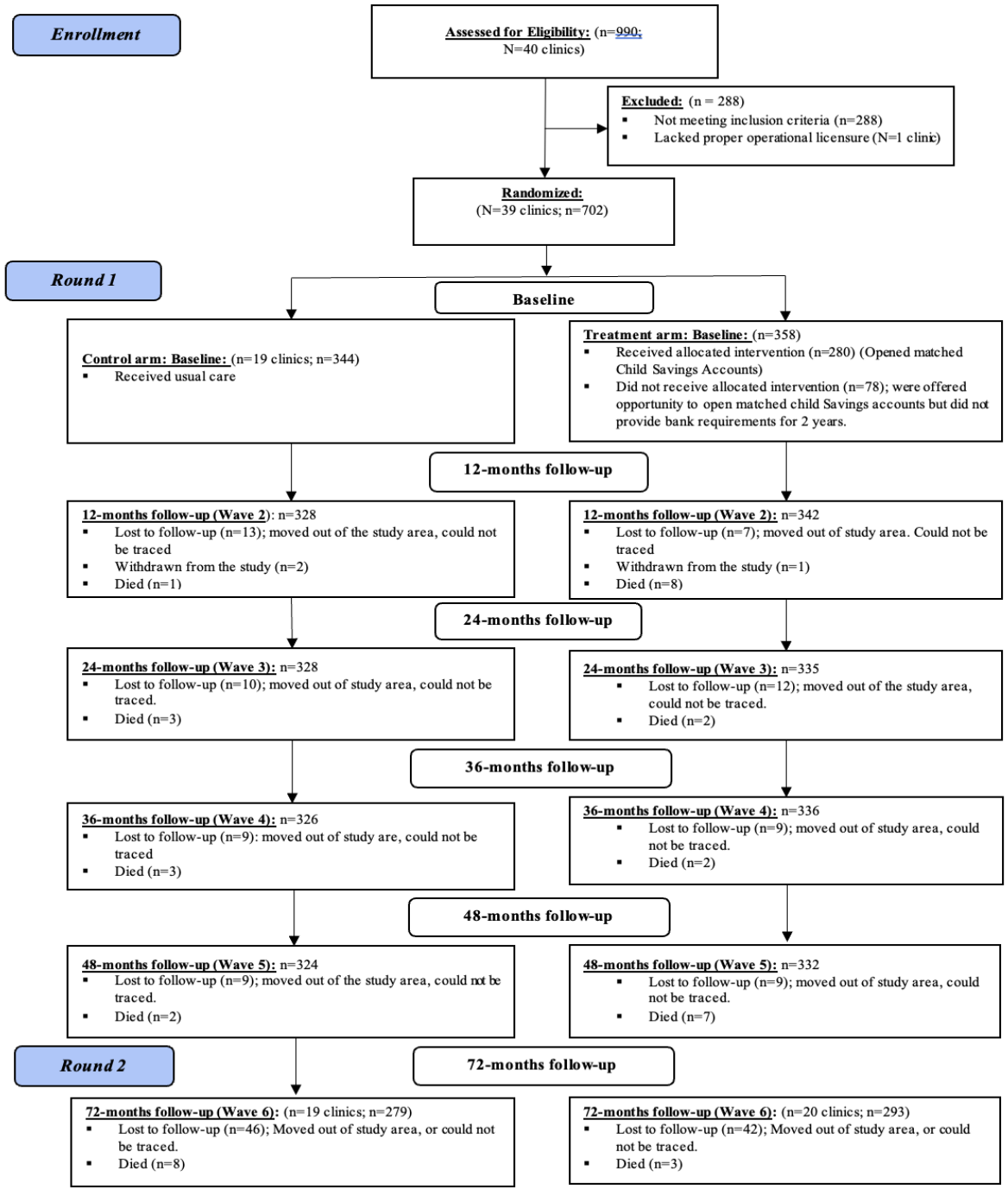
* *Statistically significant differences across the two groups*

APPENDIX D

Supplementary Table 4: Predictors selected by LASSO using MI datasets.

	MI datasets			
Predictor variable	**Dataset 2**	**Dataset 3**	**Dataset 4**	**Dataset 5**
Individual level				
Participant age				
Sex assigned at birth	x	x	x	x
The participant is in school	x	x	x	x
Adolescent works for pay	x	x	x	x
HIV stigma*				
Depressive symptoms*	x	x	x	x
Hopelessness				
Self-concept				
Adherence self-efficacy	x	x	x	x
Quality of life				
HIV/AIDS clinical knowledge (min/max: 0 to 9)				
Spline 1 (0 to 3)				
Spline 2 (4 to 6)		x		
Spline 3 (7 to 9)	x	x	x	x
Duration (years) with HIV*				
Duration (years) on ART				
Below five years				
Five to nine years				
Ten to 16 years				
Less than 5 years on ART# good ART adherence				
Five to nine years on ART# poor ART adherence		x	x	
Five to nine years on ART# good ART adherence			x	x
Ten to 16 years on ART# poor ART adherence		x		
Ten to 16 years on ART# good ART adherence		x	x	
Duration with HIV # poor ART adherence				
Duration with HIV # good ART adherence	x	x	x	x
Interpersonal level				
Communication with caregiver about HIV/AIDS				
Family cohesion (min/max: 12 to 40)				
Spline 1 (12 to 24)	x	x	x	x
Spline 2 (25 to 34)		x		
Spline 3 (35 to 40)				
Social support*				
The participant is an orphan	x	x	x	x
Number of people living in the household				
Community level				
Disclosure of HIV status	x		x	
Years at current residence (min/max: 0 to 16)				
Spline 1 (0 to 3)				
Spline 2 (4 to 9)				
Spline 3 (10 to 13)	x	x	x	x
Spline 4 (14 to 16)				
Structural level				
Household asset ownership	x	x	x	x

APPENDIX E



Supplementary Figure 1: Consort diagram for the Suubi+adherence study