

Building a Decision Model to Estimate the Health and Economic Benefits of Targeted
Mental Health Interventions to Improve ART Adherence among Young
People Living with HIV in Tanzania

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
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ABSTRACT

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Abstract

Young people living with HIV (YPLWH) constitute a growing proportion of the global population of people living with HIV but have less access to HIV testing, diagnosis, treatment, and face heightened mental health challenges. To address these challenges, targeted mental health and medication adherence interventions have been developed, including in Tanzania, which is home to 6% of the world's YPLWH. This study proposes a mathematical model to estimate the health and economic outcomes of mental health HIV adherence interventions targeting YPLWH in Tanzania.

We developed a Markov model to predict the long-term health (Disability-Adjusted Life Years (DALY)) and economic outcomes (Value of a Statistical Life Year (VLSY)) of mental health HIV adherence interventions targeting YPLWH. We parameterized the model using outcomes data from the 2016-2020 Sauti ya Vijana randomized control trial (RCT) conducted in Moshi, Tanzania. Cost data were retrieved from a cost analysis of the same RCT and supplemented with data from published literature. The study is conducted from a health payer's perspective, and the Willingness-To-Pay (WTP) per DALY averted was set to the 2021 Tanzanian GDP per capita (USD 1099.3). Costs and outcomes were modeled for ten years and discounted at an annual rate of 3%.

The findings suggest that the Sauti ya Vijana intervention modeled in this study is cost-effective at a WTP of USD 1099.3. The Incremental cost-effectiveness ratio for the

intervention compared to the standard of care was USD 637.06 per DALY averted at a 3% discount rate. The benefit-to-cost ratio of the intervention was USD 26.54 in economic productivity for the intervention arm for every dollar spent on the intervention, and the net economic productivity benefit was USD 17,174.74 over a decade.

Mental health adherence interventions hold the promise of improving health outcomes amongst YPLWH. The mathematical model developed in this study is a valuable decision-making tool for policymakers regarding mental health adherence interventions targeting YPLWH in Tanzania. The model contributes to the global goal of achieving the UNAIDS 95-95-95 targets for YPLWH.

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1. Introduction

1.1 The Burden of HIV on Young People Living with HIV

Adolescents and young people represent a growing proportion of people living with HIV worldwide. In 2020, an estimated 410,000 (27%) of all individuals who became newly infected with HIV were young people between the ages of 10 and 24 years (UNICEF, 2020; UNAIDS, 2021). Furthermore, HIV is a leading cause of death among African adolescents and young people (UNAIDS, 2015). Tanzania specifically accounts for 5.8% of adolescents living with HIV worldwide, with nearly 100,000 adolescents aged 10-19 living with HIV in 2020 (UNICEF, 2020).

Adolescents are a distinct population with unique challenges and health requirements that differ from adults and children. In addition to the physiologic bodily changes adolescents undergo, adolescents living with HIV deal with psychosocial issues, face adherence challenges in taking their HIV medications, and have to navigate sexual relationships among their peers (Lowenthal et al., 2014). Previous studies have demonstrated that people living with HIV (PLHIV) have a higher prevalence of mental health challenges (Remien et al., 2019). Mental health challenges in adolescents with HIV negatively affect adherence to antiretroviral therapy (ART), leading to worse health

outcomes (Haas et al., 2020). As such, mental health support is critical in retaining adolescents on ART and supporting their overall well-being. Due to the increasing burden of HIV on adolescents, and their need for mental health support, there have been calls for targeted strategies to improve health outcomes in adolescents living with HIV and mitigate the increase in number of new infections and AIDS-related deaths among adolescents (UNAIDS, 2015).

1.2 Mental Health Interventions targeting Young People Living with HIV

Several mental health interventions targeting young people living with HIV have been developed for the adolescent population (Bhana, Abas, Kelly, van Pinxteren, et al., 2020). For example, the community adolescent treatment supporters (CATS) intervention was designed to improve linkage and retention in care, adherence to ART, and psychosocial well-being among adolescents living with HIV in Zimbabwe. In addition to the standard of HIV care in Zimbabwe, beneficiaries of the CATS intervention receive weekly home visits during which they are provided counseling, HIV and ART information, and monitoring of ART adherence and general well-being—results from a randomized control trial (RCT) found that beneficiaries of the intervention had improved adherence and psychosocial well-being compared to adolescents who received the

standard of HIV care only (Willis et al., 2019). As another example, a pilot RCT of a local adaptation of the Collaborative HIV Prevention and Adolescent Mental Health Program Model (CHAMP) – CHAMP+ was conducted in Thailand. The Thai CHAMP+ is a group-based multifamily intervention targeting young adolescents born with HIV and their caregivers. The intervention focuses on family strengthening and addresses HIV-related challenges such as ART adherence, stigma, and identity and disclosure (Nestadt et al., 2019). In Tanzania, Sauti ya Vijana (SYV; The Voice of Youth), a group-based, scalable mental health adherence intervention, was developed to address mental health challenges and improve virologic outcomes in young people living with HIV (YPLWH) (Dow et al., 2020). SYV is delivered by young adult group leaders and helps YPLWH cope with socio-emotional distress, bolster resilience, and adhere to ART. A pilot RCT of SYV was conducted between April 2016 and August 2020 to establish the feasibility of the intervention, and a full-powered trial is currently underway in Tanzania. While the intervention has shown promising results, an economic evaluation is needed to establish its cost-effectiveness (Dow et al., 2020; Dow et al., 2022).

1.3 The Role of Health Economics in HIV Interventions and Decision-making

The discipline of health economics is crucial for decision-making in health care. Economic evaluations of public health interventions support decision-making by comparing the costs and consequences of alternative healthcare interventions and guiding policymakers to allocate scarce resources judiciously (Drummond et al., 2006; Edwards et al., 2013). Economic evaluations are increasingly being adopted in public health and HIV/AIDS research. Over the last decade, economic evaluations have been conducted on several topics in HIV/AIDS research ranging from prevention to treatment and concurrently alongside clinical trials. Furthermore, cost-effectiveness and mathematical models offer a means to estimate the health outcomes and cost benefits of various health interventions over time (Gold et al., 1996). Models have previously been used to estimate the impact of ART on the dynamics of HIV transmission (Baggaley et al., 2005; Blower et al., 2000; Baggaley et al., 2006; Eaton et al., 2012). Models have also been used to predict the cost-effectiveness of ART and pre-exposure prophylaxis in HIV prevention (Alistar et al., 2014).

The Tanzanian National Aids Control Programme (NACP) developed its fourth health sector HIV and AIDS strategic plan (HSHSP IV) in line with the UNAIDS goals to achieve the 95-95-95 targets by 2025 (95% of people who are living with HIV know their

HIV status, 95% of people who are living with HIV who know their HIV status are on ART, and 95% of all people who are on ART have suppressed viral loads) (MoHCDGEC, 2017). HSHSP IV calls for the establishment of programs to enhance retention and adherence among adolescents and youth. Economic evaluations of HIV interventions targeting this sub-population will guide policymakers in the choice of solutions to improve the UNAIDS targets in the adolescent population.

1.4 Study Justification

A systematic review of academic databases, including MEDLINE, Embase, Scopus, and the Global Index Medicus, through April 2022 was conducted to identify economic evaluations of HIV interventions targeting YPLWH that use a mathematical model. To be included, studies had to (1) involve YPLWH (10-24 years), (2) involve any diagnostic, therapeutic, behavioral, or prevention intervention for HIV (3) be an economic evaluation of any type that uses a quantitative model (4) have reported both cost and health outcomes among 10-24 year olds. All studies that did not meet these criteria were excluded. Following the search, 3,735 articles were screened, and 32 articles were included for data extraction and review. From the review, 22 studies (68.75%) were conducted in low- and middle-income countries (LMIC), while ten (31.25%) were conducted in high-

income countries (HIC). All studies conducted in LMICs were from sub-Saharan Africa, with ten originating from South Africa. Nine of the ten studies conducted in HICs were conducted in the United States, with the exception originating from England. Furthermore, all but two studies performed a cost-effectiveness analysis, with the exceptions performing a cost-utility analysis and a combination of cost-effectiveness and cost-utility analysis, respectively. The breakdown by HIV intervention was as follows: six (19%) evaluated male circumcision, six (19%) a mental, behavioral, or educational intervention, five (16%) HIV testing, five (16%) a combination of interventions, four (13%) pre-exposure prophylaxis, three (9%) an HIV vaccine, one (3%) long-acting antiretroviral therapy (ART), one (3%) condom distribution, and one (3%) mobile ART adherence reminders. The overview of models found in the review was as follows; seven studies used a compartmental model, four a microsimulation model, three a Markov model, one a network model, and 17 other mathematical models. It was found that few studies evaluated interventions designed to help YPLHW cope with HIV, and no study explored mental health using models. Furthermore, only 11 models accounted for medication adherence (Zimmerman et al., 2022 (unpublished)) (See Appendix 1). The search did not yield an appropriate quantitative model applicable to mental health ART adherence interventions. In addition, the most applicable of the models reviewed were

proprietary and inaccessible (Ciaranello et al., 2013). Hence, we developed the Markov microsimulation model.

1.5 Study Aims and Objectives

This study aimed to develop a decision model to estimate the long-term health and economic benefits of mental health ART adherence interventions targeting YPLWH. To achieve our aim, we had the following objectives (1) to determine the per patient annual costs of delivering a mental health HIV adherence intervention to YPLWH in Tanzania, (2) to develop a Markov microsimulation model to estimate the costs and benefits of mental health adherence interventions for YPLWH. Consequently, we hope to guide policy change and resource allocation regarding the control of HIV and ultimately contribute to improving health outcomes among YPLWH and reducing the spread of HIV in Africa.

2. Methods

We developed a mathematical model to answer the research question– What are the long-term health and economic benefits of mental health adherence interventions targeting YPLWH? While our research question focused on mental health adherence intervention in YPLWH, we parameterized the model using the best available data – the SYV 2016-2020 pilot study conducted in Tanzania (Dow et al., 2022). This study qualified as non-human subject research as it is a secondary data analysis using de-identified patient data and was exempt from an institutional review board.

2.1 Setting and location

Tanzania is a lower-middle-income country in east Africa (World Bank, 2022). The country has an estimated population of 64 million, with over half the population aged 19 years and younger (Njakoi, 2021). The focus of our research is on YPLWH living in Tanzania where, per the national guidelines, clinically stable patients (virally suppressed) are scheduled for clinic visits every six months for ART refills and viral load tests once a year. On the other hand, individuals who are not clinically stable and suspected of failing treatment are scheduled for monthly clinic visits and receive adherence counseling at each visit. According to the national guideline, YPLWH are expected to receive psychological

support through peer support groups and counseling every month from dedicated adolescent HIV clinics; however, not all YPLWH benefit from these services (Dow et al., 2019; MoHCDGEC, 2017). A scoping review of adolescent mental health interventions in sub-Saharan Africa found SYV to be the only intervention targeting YPLWH in Tanzania (Mabrouk et al., 2022). However, other interventions addressing mental health and medication adherence have been developed for YPLWH in the country (Njau et al., 2022).

SYV was piloted in Moshi, Tanzania, between 2016-2020 to establish the feasibility and acceptability of the intervention in preparation for a fully powered effectiveness trial. Moshi, Tanzania, is a municipality and the capital of the Kilimanjaro region in Northeast Tanzania. The city is a hub for government activities, banking, trade, and tourism (Madenge, 2021). Moshi municipality had a population of 184,292, while the rural districts – had 466,737, according to the 2012 population census. The participants were recruited from adolescent HIV clinics at the Kilimanjaro Christian Medical Centre (KCMC) and Mawenzi Regional Referral Hospital in Moshi, Tanzania. The intervention was delivered to all participants in a neutral facility – Kilimanjaro Clinical Research Institute (KCRI) satellite facility, Majenjo, Moshi (Figure 1).

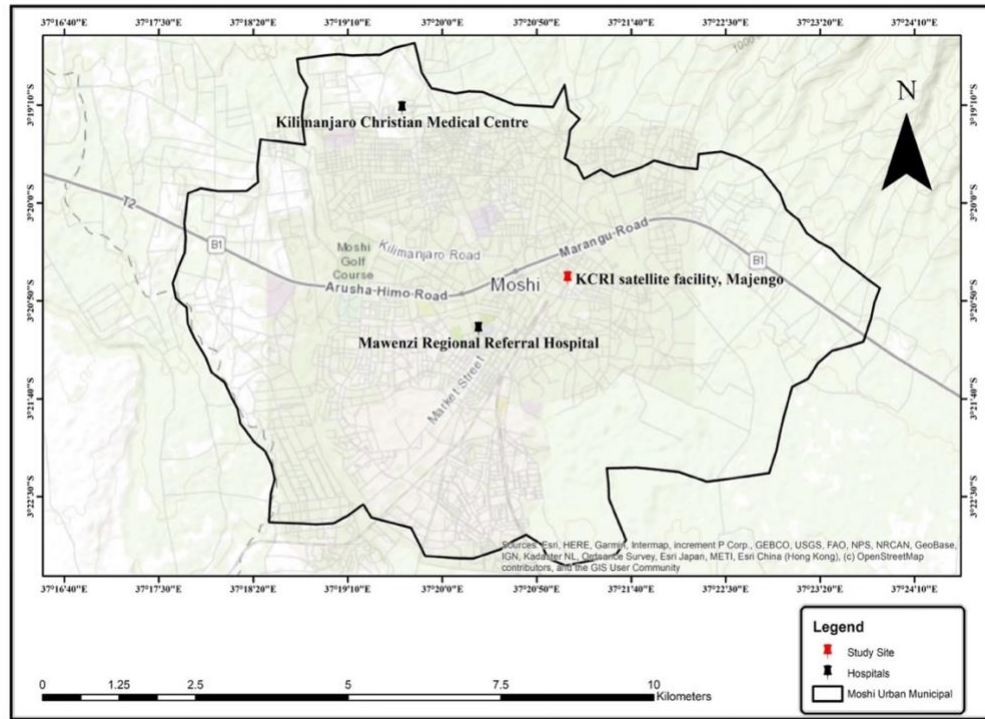


Figure 1: Map of Moshi urban area showing participant recruitment hospitals and study site

2.2 Study population

The model is designed for YPLWH living in Tanzania and parameterized using SYV data. Young people aged 10-24 comprise a significant portion of the Tanzanian population, accounting for approximately 17 million of the overall population of nearly 64 million (Worldbank, 2019; TACAIDS, 2017). In 2019, the prevalence of HIV in young people aged 10-24 was estimated at approximately 1% or 180,355 individuals, the

incidence was about 13,401 individuals or 0.074 per person year, and the death toll was approximately 3,347 individuals (IHME, 2019). The 2016-2017 Tanzania HIV impact survey (THIS) revealed that only 50% of YPLWH aged 15-24 years were aware of their HIV status, 92.6% of those aware were on ART, and 83.5% were virally suppressed (TACAIDS, 2017). The survey highlighted the gap in adolescent HIV care as progress to achieve the UNAIDS targets were lower in YPLWH compared to adults 15 years or older of whom 61% were aware of their HIV status, 93.6% of those aware were on ART, and 87% virally suppressed.

The SYV pilot study population consisted of young people aged 10-24 years living with HIV who were aware of their HIV status. Additional inclusion criteria for the participants included their availability to participate in the study and understand the intervention. The SYV study enrolled 128, with 105 eventually randomized into the intervention (58 participants) or standard of care arm (47 participants). We used participant data from the SYV pilot RCT to parameterize the model.

2.3 Intervention and comparators

Interventions targeting YPLWH range broadly from family-level interventions focusing on family-strengthening parenting interventions targeting adolescents and their

caregivers to group-based interventions delivered via adolescent peer support groups and less frequently individual mental health interventions (Bhana, Abas, Kelly, Pinxteren, et al., 2020). SYV is a ten-week group-based intervention delivered over ten 90-minute group sessions, with two sessions involving the participants' caregivers and two individual sessions with the group leaders. SYV sessions were designed with input from youth advisors and included components of evidence-based models of Cognitive Behavioral Therapy, Interpersonal Psychotherapy, and Motivational Interviewing. The SYV pilot RCT compared SYV + the standard of adolescent HIV care to the standard of adolescent HIV in Moshi. The standard of care for adolescents living with HIV in Tanzania consists of routine visits to adolescent HIV clinics where individuals receive free antiretroviral medication, periodic viral load tests, and HIV counseling with adherence counselors for virally unsuppressed individuals (MoHCDGEC, 2017; Forsythe et al., 2019).

2.4 Procedures and measures

In the SYV pilot RCT, participants responded to structured interviews, and outcome measures were collected from the treatment arm at baseline, 6-month follow-up, 12-, 18-, and 30-month follow-up. Constructs measured in the study included depression using the Patient Health Questionnaire (PHQ-9), emotional and behavioral symptoms,

post-traumatic stress, ART adherence, and viral suppression. We utilized ART adherence and viral suppression data from the pilot RCT for this modeling study.

2.4.1 Antiretroviral therapy adherence

In the SYV pilot RCT, ART adherence was a secondary outcome that was measured subjectively by participants' self-report using a 3-item adherence measure that is converted to a 0-100 scale with zero being the worst adherence to ART and 100 the best (Wilson et al., 2016). A 7.29, [95% CI, 2.24, 12.33] unit increase in self-reported adherence was recorded in SYV participants six months after the delivery of the intervention. We defined an adherent patient as an individual with a self-reported adherence score of 50 and above. We used this threshold as the traditional adherence thresholds of 80/90 yielded abysmally low adherence rates in both cohorts of the SYV study. Estimates of adherence used in the model are provided in Table 1.

2.4.2 Viral suppression

The primary outcome of the SYV study was the proportion of virally suppressed adolescents six months after the delivery of the intervention. Secondary study outcomes included participants' HIV RNA viral load levels at other time points (12, 18, and 30

months). Virologic failure was defined as plasma HIV RNA level > 400 copies/ml. The risk ratio for virologic suppression in the intervention arm compared to the standard of care arm was 1.15 [95% CI, 0.95, 1.39] at six months, 1.17 [95% CI, 0.92, 1.48] at 12 months, and 0.99 [95% CI, 0.76, 1.31] at 18 months (Dow et al., 2022).

2.5 Measurement and valuation of resources

We determined the per patient cost of delivering a mental health adherence intervention to YPLWH in Tanzania by conducting a cost analysis of the 2016-2020 SYV RCT. A hybrid costing approach was used to determine the cost of delivering the SYV intervention. In addition, we employed an intent-to-treat approach in our analysis where we assumed that all 58 participants in the intervention arm received treatment and were followed up at the 5 study time points. Using a health provider's perspective, we conducted a retrospective cost analysis of the 2016-2020 SYV pilot trial to determine the per-patient cost of SYV delivery. Costs were collected from project ledgers and through consultations with key RCT personnel. Intervention costs comprised the direct costs, such as intervention training and delivery, and the indirect costs - overhead and administrative costs. We measured labor input in full-time equivalent for salaried personnel (see Table 7 in Appendix C). We estimated the costs of SYV delivery in two scenarios. In the first

scenario, we determined the cost of SYV delivery to the 58 participants in the treatment arm. In the second scenario, we costed SYV delivery to all 105 participants, following the delivery of SYV to the SOC participants in three subsequent crossover waves (Fig 2) (see Tables 8 & 9 in Appendix C) (Fawole et al., 2022 (unpublished)). We parameterized intervention costs in the model using the cost per participant per year.

Costing Scenario		Quarter	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	
		Year	2016			2017				2018				2019				2020		
Scenario 1	Wave 1 - SYV	X	T	X	I	X	I	X	I	I	I	I	X	I	I	I	I	I	I	I
	Wave 2 - SYV			X	T	X	I	X	I	X	I	I	I	X	I	I	I	I	I	I
	Wave 3 - SYV				X	T	X	X	I	X	I	X	I	I	I	I	X	I	I	I
	Wave 4 - SOC	C	C	C	C	C	X	T	X	I	I	I	I	I	I	I	I	I	I	I
	Wave 5 - SOC	C	C	C	C	C	C	C	C	C	C	C	C	X	T	X	I	I	I	I
	Wave 6 - SOC	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	X	T	X	

Figure 2: SYV stepped-wedge study design and costing approach (Legend: X= quantitative data collection from study participants, T= Ten-week delivery of SYV intervention, I= Indicates study wave has received the SYV intervention, C= Indicates RCT control arm)

2.6 Currency, price date, and conversion

We recorded RCT costs in Tanzanian Shillings and US dollars where appropriate and converted them to the 2022 US dollar equivalent. All other costs included in the model were updated to the 2022 US dollar using the Consumer Price Index inflation calculator.

2.7 Rationale and description of the model

We developed a Markov decision-based cohort simulation model in TreeAgePro Healthcare Version 2022 to predict the health and economic benefits of mental health adherence interventions. We structured the model around three mutually exclusive and collectively exhaustive health states. The health states include 'Alive & virally suppressed,' 'Alive, not virally suppressed,' and 'Dead.' Figure 3 shows the state transition diagram, and Figure 4 shows the basic event pathway of the model. Individuals in the 'Alive & virally suppressed' and 'Alive, not virally suppressed' health states can either be ART Adherent or ART nonadherent and change between these health states over time or die. When individuals in the model die, they move to the 'Dead' health state, which serves as the accumulator. We included trackers in the model to determine the

average length of time each cohort spent in the Alive & virally suppressed and ART-adherent states.

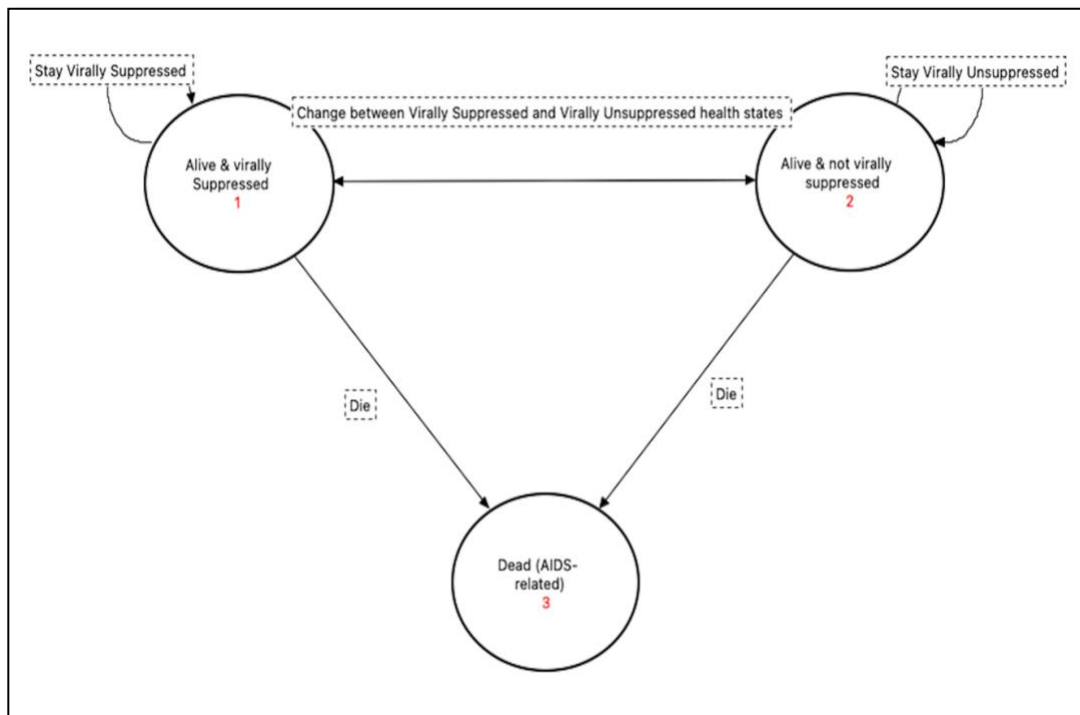


Figure 3: State transition diagram of the Strategies: circles represent health states, and arrows represent the possible transition between different health states.

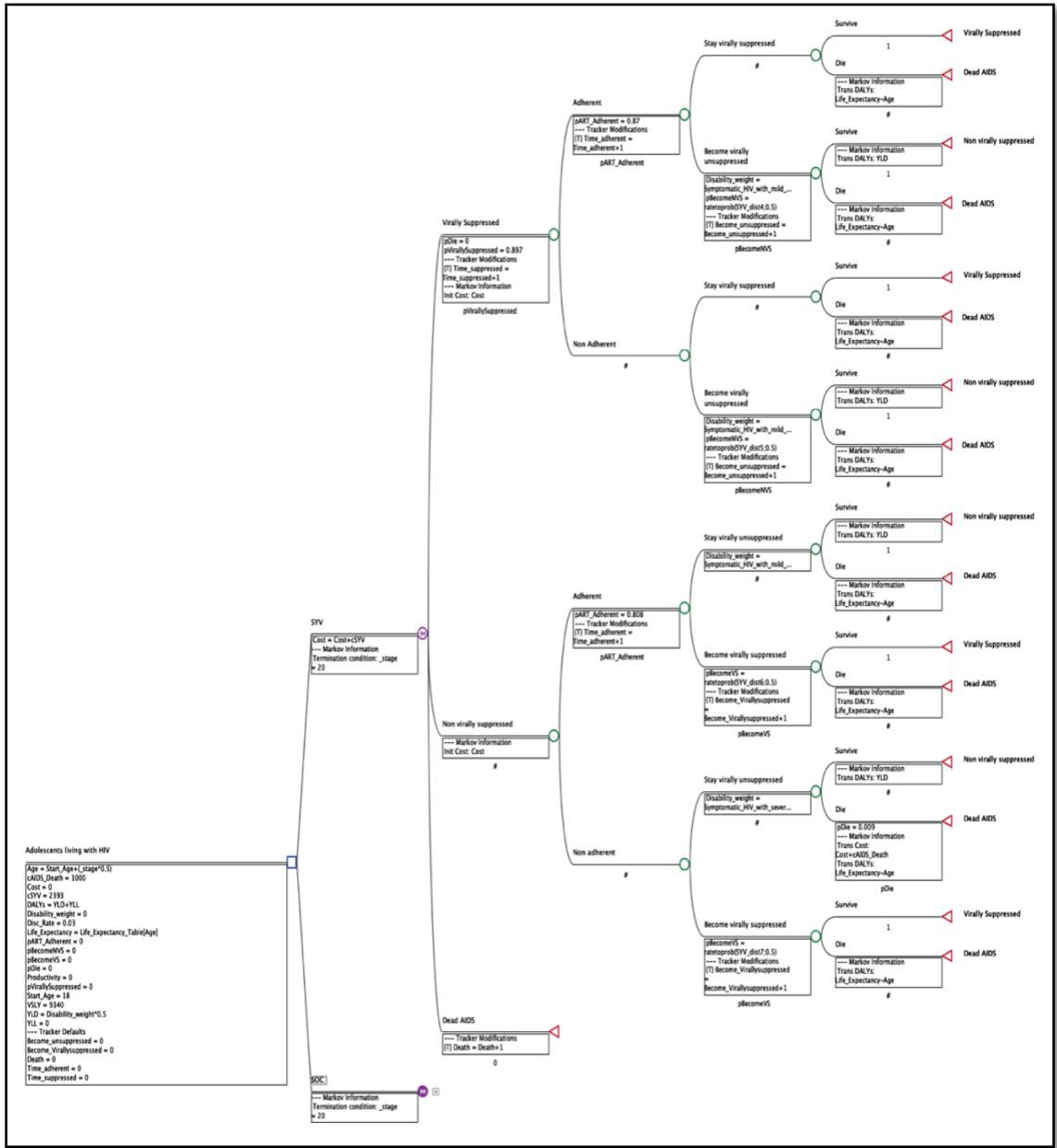


Figure 4: Model event pathway (Markov tree diagram): Showing two strategies SYV and SOC (Does not reflect actual parameterization of the model)

2.8 Transition rates and probabilities

We obtained the model transition probabilities from the SYV pilot study (2016-2020). The SYV pilot study data was cleaned and managed using R Studio software version 2022.07.1 Build 554 and Microsoft Excel version 16.64. We determined the probabilities that individuals in either arm of the study were (1) Alive & virally suppressed and ART adherent, (2) Alive & virally suppressed and ART nonadherent, (3) Alive, Not virally suppressed and ART adherent, (4) Alive, Not virally suppressed and ART nonadherent. We then determined the rate at which individuals in the states, as mentioned earlier, changed viral suppression status, i.e., from Alive & virally suppressed to Alive, Not virally suppressed, and vice versa, or stayed in the same viral status at the next follow-up point in the SYV study. We made assumptions about the transition rates for the period following the end of the RCT and modeled a scenario using the transition rates from the 12th to 18th month of the SYV RCT in subsequent stages of the analysis, i.e., from the 18th month to the 10th year. All rates were converted to transition probabilities. Details of the calculation of transition probabilities are provided in Appendix D. For the calculation of the probability of death, we used time-to-event analysis to calculate the 6-month risk of death in both arms of the study. In the model, we assumed only Alive & virally unsuppressed and ART nonadherent individuals who stay

Alive & virally unsuppressed in a given cycle could die; hence we applied the 6-month risk of death to the associated model branch in both cohorts.

Table 1: Cost-effectiveness inputs (Markov)

Variable description	Value	References
Start age of modeled cohort	18	Estimated
Current age = Start age + (_stage*0.5)	-	Estimated
Cost of SYV	USD 701.68	(Fawole et al., 2022 unpublished)
Value of statistical life year	USD 9340	(Patenaude et al., 2019)
Cost of ART support services for individuals who are alive and virally suppressed	USD 44	(Forsythe et al., 2019)
Cost of ART support services for individuals who are alive and not virally suppressed	USD 132	Estimated
Utility weight ART adherent & virally suppressed	0.277	Weights (Ackerman et al., 2022)
Utility weight ART non adherent and alive virally suppressed	0.381	Weights (Ackerman et al., 2022)
Probability of death in the SYV arm	0.009	Calculated using RCT data from (Dow et al., 2022)
Probability of death in the SOC arm	0.0183	Calculated using RCT data from (Dow et al., 2022)
Life expectancy of modeled cohort	72.6	(WHO, 2019)
Probability individuals in the standard of care arm are alive & virally suppressed	0.67	Calculated using RCT data from (Dow et al., 2022)

Probability individuals in the standard of care arm who are alive & virally suppressed are ART adherent	0.698	Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the standard of care arm who are alive & not virally suppressed are ART adherent	0.723	Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the SYV arm are alive & virally suppressed	0.649 at baseline, 0.745 at six months, 0.755 at 12 months, 0.694 at 18 months and above	Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the SYV arm who are alive & virally suppressed are ART adherent	0.838 at baseline, 0.902 at six months, 0.769 at 12 months, 0.970 at 18 months and above	Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the SYV arm who are alive & not virally suppressed are ART adherent	0.8 at baseline, 0.929 at six months, 0.769 at 12 months, 0.733 at 18 months and above	Calculated using RCT data from (Dow et al., 2022)
Probability an individual in either SYV or SOC who were Alive & Not virally suppressed become Alive and Virally suppressed based on their ART adherence status		Calculated using RCT data from (Dow et al., 2022)
Probability an individual in either SYV or SOC who were Alive & virally suppressed become Alive & Not virally suppressed based on their ART adherence status		Calculated using RCT data from (Dow et al., 2022)

2.9 Selection, measurement, and valuation of outcomes

We valued health outcomes in terms of the impact of disability-adjusted life years (DALYs) on viral load suppression. We obtained disability weights from the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease Study 2019 (GBD 2019) Disability Weights (Ackerman et al., 2022). The calculation of the years lost to disability was done using a disability weight of 0.277 (0.189-0.379), representing individuals living with HIV who are mildly symptomatic but pre-AIDS and have anemia. We applied the disability weight to the following branches in the model (1) Alive & virally suppressed and either ART adherent or nonadherent, who change health states (2) Alive, Not virally suppressed and adherent, who remain virally unsuppressed. We applied a disability weight of 0.381 (0.269-0.505) representing individuals living with HIV who are severely symptomatic but pre-AIDS and anemia to the Alive, Not virally suppressed, and ART non-adherent who stay virally unsuppressed branch of the model. Years of life lost were calculated by subtracting the age at death from the life expectancy for that age. Life expectancy data was obtained from the World Health Organization's Global Health Estimates (WHO, 2019).

We captured economic benefits or productivity outcomes using the value of a statistical life year (VSLY) from a population-based survey conducted in Tanzania

(Patenaude et al., 2019). VSLY was calculated as a function of DALYs; specifically, the years lost to disability in the virally suppressed and unsuppressed health states. Additionally, we included the cost of HIV treatment support services in Tanzania in our model. We applied the average value of treatment support to the Alive and Virally suppressed state and assumed a higher cost for the Alive, Not virally suppressed health state (Table 1). The cost estimates for HIV treatment support services were retrieved from a costing survey conducted in Tanzania (Forsythe et al., 2019).

2.10 Perspective, time horizon, and discount rate

This study is conducted from a societal perspective. The model has a 10-year time horizon and a cycle length of 6 months to correspond with the data collection time points of the SYV pilot study (2016-2020). We discounted costs and outcomes at a rate of 3% per year and conducted sensitivity analyses around discount rates of 0% and 5%.

2.11 Model validation

We conceptualized the model and refined the computerized version with input from expert health economists with significant experience in health technology assessments and mathematical modeling. In addition, the experts reviewed the input data

for its appropriateness, noting shortcomings where found. To ensure the accuracy and reliability of our model, we employed systematic validation procedures using the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool (Vemer et al., 2016). We performed several validation exercises, including structural and internal checks, and ran simulations using extreme values on select parameters to detect aberrant behavior. Trace testing was conducted to identify the movement of participants in the model, and trackers were used to monitor the time spent in the viral suppression, ART adherence, and death health states. Values derived from the testing were compared to what was expected, and the model was found to behave predictably.

2.12 Sensitivity analysis

We conducted a deterministic one-way sensitivity analysis around the discount rate and reported the estimates obtained from a discount rate of 0% and 5%. Additionally, we ran 1000 iterations of a microsimulation to account for uncertainty in our calculations. To explore uncertainties around the intervention cost and ART adherence estimates, we conducted a two-way microsimulation sensitivity analysis where we modeled a 10% increase and decrease in the cost delivery of SYV and a 10% increase and decrease in the ART adherence rates of both study arms. Lastly, we conducted 1000 iterations of

probabilistic sensitivity analysis with 1000 iterations of microsimulations around the distributions of five parameters, including the self-reported adherence estimates, cost of intervention delivery, viral suppression estimates, the cost of HIV support services to individuals not virally suppressed, and the disability weights (See Appendix D).

2.13 Study parameters

Variables utilized in the model included a starting cohort age of 18 years. In both cohorts, we applied a disability weight of 0.277 to Alive & virally suppressed individuals who become Alive & Not virally unsuppressed in the next cycle and 0.381 to individuals who are Alive, Not virally suppressed, who remain Alive but not virally suppressed. For the VSLY, we applied a value of USD 10,432.25 per annum to both study arms. Additionally, we applied the intervention cost to the SYV cohort in the model, using the lower bound of the per patient cost of SYV delivery per annum – USD 701.68. We modeled the cost of HIV support services and applied a cost of USD 44 per annum to the Alive & virally suppressed health state, and assumed a value of USD 132 per annum to the Alive, Not suppressed health state. The probabilities of viral suppression and ART adherence were inputted based on the values derived for each time point in the SYV study for the intervention arm. We utilized the values from the last available data collection time point

in the SYV RCT for the period following the trial. The average values of viral suppression and ART adherence across all time points were used for the SOC cohort. The probability of death was 0.009 in the SYV cohort and 0.0183 in the SOC cohort (See Table 1.).

3. Results

3.1 Study findings

Based on the Markov model described above, the SYV cohort spent on average 8.92 [95% CI, 8.78, 9.06] years adherent to ART compared to 6.87 [95% CI, 6.61, 7.14] years in the SOC cohort, out of a possible ten years. Additionally, the average number of years spent Alive & virally suppressed was 7.18 [95% CI, 6.78, 7.85] years in the SYV cohort, compared to the SOC at 6.77 [95% CI, 6.00, 7.54] years. Compared to the standard of care cohort, the incremental cost-effectiveness ratio (ICER) for the SYV cohort was approximately USD 547.19 per DALY averted at a 3% discount rate. A benefit-cost analysis of the intervention costs and resulting productivity gains showed that the SYV intervention yielded a benefit-to-cost ratio of USD 26.54 in economic productivity over ten years for every dollar spent on the intervention. Further, the net economic productivity benefit of the SYV cohort was USD 17,174.74 over a decade. The microsimulation showed a 3% cohort death in the SOC cohort and 1% in the SYV, resulting in an incremental cost per death averted of USD 322 (Table 4).

The results from the deterministic analysis show that the ICER over ten years for SYV compared to SOC was approximately USD 547.68 per DALY averted at a 3% discount rate, illustrating that the SYV intervention is very cost-effective as the estimated ICER is

less than the WTP, Tanzania's gross domestic product (GDP) per capita for 2021 – USD 1099.3 (World Bank, 2021) (Table 2).

3.2 Sensitivity analysis

Results from the one-way sensitivity analysis showed that at a discount rate of 5%, the ICER was USD 597.68 per DALY averted; without discounting costs and effectiveness, the ICER was USD 474.03 per DALY averted. Table 2 below shows the cost-effectiveness results calculated at 0%, 3%, and 5% discount rates. Results from the two-way sensitivity analysis showed that the ICER ranged from USD 361.12 per DALY averted in the best-case scenario, following a 10% increase in the average ART adherence scores in both cohorts and a 10% decrease in SYV delivery costs to USD 855.86 per DALY averted in the worst-case scenario following a 10% decrease in the average ART adherence scores in both cohorts and a 10% increase in SYV delivery costs (Table 5). Furthermore, the probabilistic sensitivity analysis with microsimulation revealed that the intervention was the optimal strategy in 83.2% of the iterations at the WTP, and the estimated ICER was USD 637.06 per DALY averted [95% CI, 631.40, 642.71] (Fig. 5). The cost-effectiveness acceptability curve further showed that the intervention achieved a 90% probability of cost-effectiveness at a WTP of \$1600 (Fig. 6)

Table 2. Cost-effectiveness table showing sensitivity analysis at 0%, 3%, and 5% discount rates.

Discount rate	Strategy	Cost (USD)	Incremental Cost (USD)	Effectiveness (DALYs)	Incremental Effectiveness	ICER (USD)	Productivity (USD)
0%	SOC	647	0	2.50	0	0	74,4485.33
	SYV	1294	647	1.13	1.37	474.03	94,622.60
3%	SOC	564	0	2.19	0	0	65,014.52
	SYV	1219	655	0.99	1.20	547.19	82,398.95
5%	SOC	518	0	2.02	0	0	59,740.68
	SYV	1178	660	0.92	1.92	597.68	75,596.54

The SYV and SOC strategies were undominated at 0%, 3%, and 5% discount rates.

Table 3. Microsimulation results (1000 iterations at a 3% discount rate) –
 Showing costs, DALYs, and productivity gains of the modeled strategies.

Statistic	Cost in USD (SYV)	Cost in USD (SOC)	DALYs (SYV)	DALYs (SOC)	Productivity in USD (SYV)	Productivity in USD (SOC)
Mean	1283 [95% CI, 1272, 1294]	639 [95% CI, 620, 657]	1.00 [95% CI, 0.76, 1.25]	2.18 [95% CI, 1.73, 2.62]	82,229.99 [95% CI, 81,737.67, 82,722.31]	65,484.25 [95% CI, 64,788.90, 66,179.60]

Table 4. Microsimulation results (1000 iterations conducted at a 3% discount rate) –
 Showing the average amount of time each cohort spent ART adherent, Alive & virally suppressed, and the deaths recorded over ten years.

Statistic	Average time spent ART adherent (SYV) in years	Average time spent ART adherent (SOC) in years	Average time spent Alive & virally suppressed (SYV) in years	Average time Alive & virally suppressed (SOC) in years	Death (%) (SYV)	Death (%) (SOC)
Mean	8.92 [95% CI, 8.78, 9.06]	6.87 [95% CI, 6.61, 7.14]	7.18 [95% CI, 6.78, 7.85]	6.77 [95% CI, 6.00, 7.54]	1 [95% CI, 0.31, 1.49]	3 [95% CI, 2.2, 4.4]

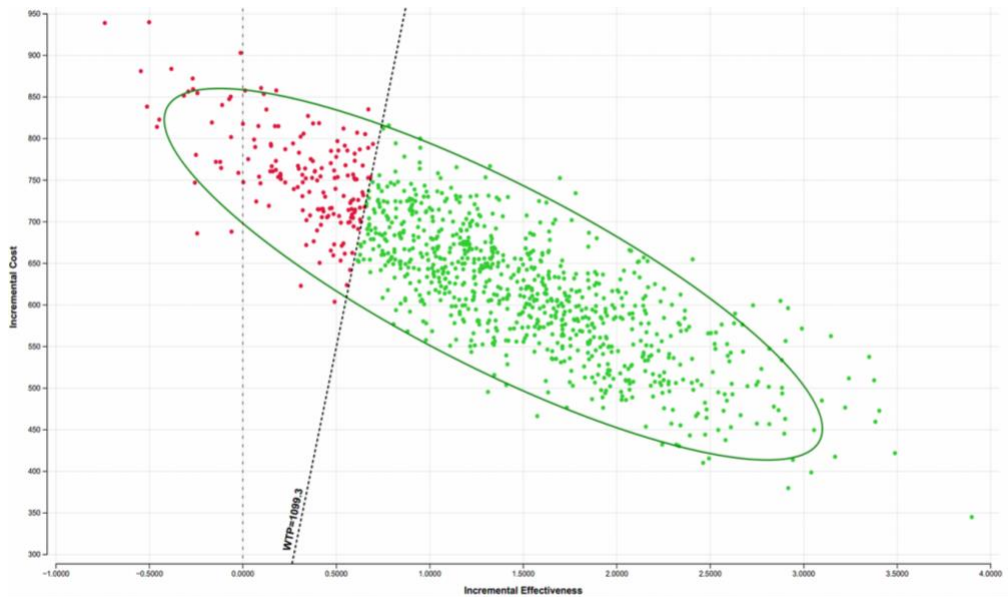


Figure 5: Incremental cost-effectiveness scatterplot, SYV v. SOC.

Willingness to pay set at 2021 Tanzanian gross domestic product USD 1099.3. Eclipse represents a 95% confidence interval. Green dots represent iterations/ICERs of the probabilistic sensitivity analysis that were cost-effective while red dots represent iterations that were not cost-effective demarcated by the WTP threshold. Scatterplot shows SYV was cost-effective in 8320 of 1000 iterations.

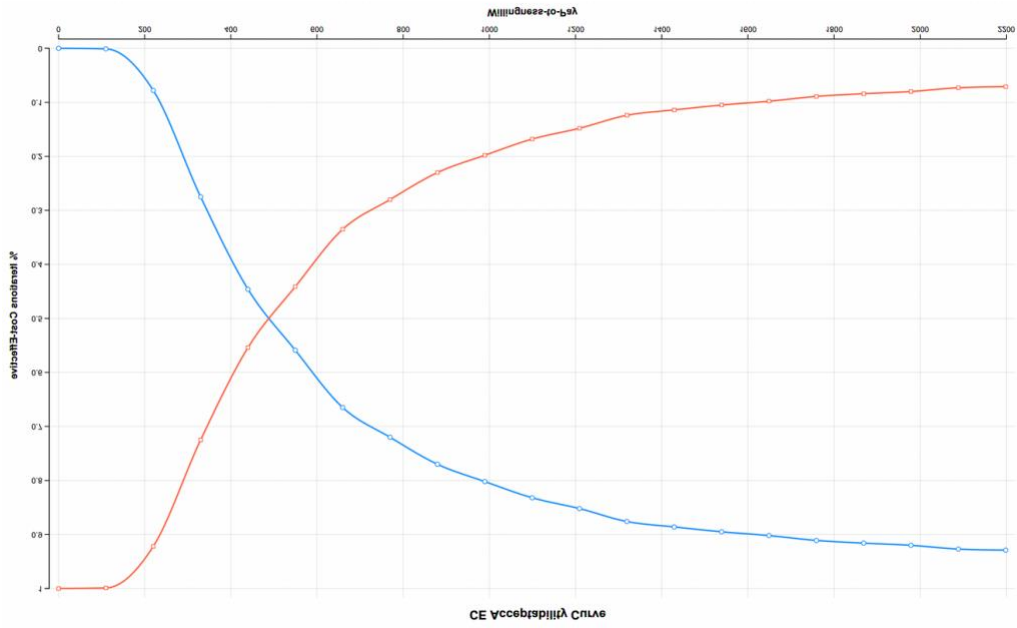


Figure 6: Cost-effectiveness acceptability curve (CEAC) – Showing the probability of cost-effectiveness (Y-axis) over a range of WTP (X-axis) for the modeled cohorts. The blue line represents the SYV cohort, while the red line represents the SOC cohort

Table 5: Two-way microsimulation sensitivity analysis – showing the best- and worst-case scenarios around ART self-reported adherence and cost of the intervention delivery estimates.

Scenario	Strategy	ICER (USD)
Best-case	10% decrease in the cost of intervention delivery & 10% increase in adherence estimates	356.56
Worst-case	10% increase in the cost of intervention delivery & 10% decrease in adherence estimates	844.76

4. Discussion

The primary aim of this study was to develop a model capable of estimating the long-term health and economic benefits of mental health adherence interventions targeting YPLWH. To our knowledge, this is the first model designed specifically to estimate the benefits of mental health interventions targeting YPLWH in Tanzania.

Results from the probabilistic sensitivity analysis of the model show that the ICER over ten years for SYV compared to SOC was approximately USD 637.06 per DALY averted at a 3% discount rate. Per our findings and according to the WHO guidelines on Choosing Interventions that are Cost Effective (WHO-CHOICE), SYV can be considered a very cost-effective approach as it is less than the WTP – 2021 GDP per capita of Tanzania (WHO, 2001). Furthermore, the intervention yielded a benefit-to-cost ratio of USD 26.54 in economic productivity for the SYV cohort over ten years for every dollar spent on the intervention, highlighting the long-term social benefits of SYV. Our analysis also showed that the choice of discount rate did not significantly impact the estimated ICER of the intervention as SYV was cost-effective without discounting costs and outcomes and at a discount rate of 5%. Results from the cost analysis of the SYV RCT showed that cost per participant per year decreased from USD 1,231.23 for 58 participants to USD 701.68 for

105 participants, suggesting that the costs of the intervention may likely decrease with larger-scale delivery to YPLWH (see Appendix C).

Because the SYV pilot study was not powered to detect a treatment effect, we sought to increase confidence in our effectiveness estimates and the model results by reviewing the literature to identify other mental health ART adherence interventions targeting YPLWH. We identified several studies, including the Ziphamandla intervention in Tanzania, the Champ+ intervention in Thailand, the CATS/Zvandiri intervention in Zimbabwe, the Imbereheza project in Rwanda, and the VUKA family program in South Africa (Andersen et al., 2018; Willis et al., 2019; Nestadt et al., 2019; Donenberg et al., 2022; Bhana et al., 2014). We found that none of the studies utilized an objective measure of adherence, and they employed various methods of assessing self-reported adherence, such as visual analog scales. Furthermore, the studies differed in contextual background, and most evaluated the acceptability and feasibility of their interventions. The significant differences across the contextual background, study design, target population, methods employed as well as limited access to their RCT data did not permit the triangulation of effectiveness estimates. Nevertheless, the findings from the model show that mental health adherence interventions such as SYV show promise of increased health and economic benefits to YPLWH and the general society.

The parameterization of the mathematical model we developed using multiple studies and RCTs of mental health adherence interventions targeting YPLWH that are powered to evaluate treatment effectiveness and utilize objective measures of ART adherence over multiple follow-up time points will make the results more generalizable. Results from the forthcoming multicenter SYV RCT in Tanzania may meet these requirements.

Comparing our study findings to other published work proved challenging as, to our knowledge, most mental health adherence interventions targeting YPLWH did not have an accompanying cost-effectiveness analysis or explore the benefits of their respective interventions using a mathematical model. An exception was the CATS/Zvandiri intervention that performed a cost-effectiveness analysis which showed that the annual cost per adolescent treated through Zvandiri intervention clinics was USD 997 per annum and the cost per virally suppressed adolescent on ART was USD 1,340 per annum (Mavhu et al., 2020). Furthermore, the systematic review we conducted, which sought to identify economic evaluations of HIV interventions targeting YPLWH that use a mathematical model, yielded a study that modeled medication adherence for youth living with HIV in the United States but was not specifically a mental health intervention. The study used a microsimulation model to explore the benefits of a hypothetical 12-

month adherence intervention that improves virologic suppression by ten percentage points over the standard of care. The model results showed that the hypothetical intervention resulted in an ICER of USD 7,900 per quality-adjusted life-year (Neilan et al., 2021). Given that the adherence intervention in the study was hypothetical and focused on YPLWH in a high-income setting, the study results are not an ideal comparison for our model results.

Stakeholders, including researchers, international health agencies, and national programs, have called for targeted strategies to improve health outcomes among YPLWH. However, there are limited interventions to support YPLWH, and few studies have explored the economic and health implications of implementing and scaling such interventions for this age group. This study responds to this call and adds valuable information as well as highlighting limitations in extant literature. It is our expectation that the finding will help the government of Tanzania and similarly resourced countries to guide decision-making and improve the lives of YPLWH. Additionally, mental health ART adherence initiatives for YPLWH align well with the UNAIDS 95-95-95 global target, which aims to have 95% of all people living with HIV diagnosed, 95% of all people diagnosed with HIV on antiretroviral therapy, and 95% of all people with HIV on antiretroviral therapy virally suppressed by 2030 (UNAIDS, 2017)

4.1 Study strengths and limitations

This study had a few strong points and limitations. Firstly, throughout the development process, we collaborated with expert health economists to conceptualize and refine the model and used the AdViSHE tool to validate the model. Other strengths of the study include the parameterization of the model using longitudinal data from the SYV RCT, which lends credence to the validity of the results. Hence, we captured the immediate benefits of the intervention and the loss of treatment effects in the intervention arm over time in our analysis. Additionally, we parameterized the model using cost data relevant to the Tanzanian context of HIV care, including the cost of delivering a mental health adherence intervention, HIV support services, and the value of a statistical life year in Tanzania.

Our study had some limitations. Firstly, the SYV pilot study was a small clinical trial that was not powered to detect a treatment effect. Consequently, the number of participants in the study, particularly the control arm, failed to provide robust data for the analysis. The low number of participants was particularly evident during the trial's follow-up period, where the number of participants in the control arm declined significantly. To mitigate this challenge, we used the average estimates of viral suppression and ART adherence from the SOC arm recorded over the RCT data collection

time points. Secondly, we used self-reports of ART adherence to capture changes in adherence states over time. Adherence self-reports are known to be subject to bias and have a weaker correlation to viral suppression than objective measures. Thus, we conducted sensitivity analyses around our estimates.

To calculate the economic benefits of the intervention, we used the average value of a statistical life year in Tanzania, which may exaggerate the results for this age group as the starting age of our modeled cohort is 18 years old. Furthermore, our model fails to fully account for the compounding of the economic benefit of the intervention over time as individuals age. Given the limitations of this study imposed by the sample size of the pilot study, the results of the fully powered SYV RCT currently underway will be essential to provide more robust results to which the mathematical model developed herein will be applicable.

Nonetheless, this study, the first to be conducted in Tanzania, adds great value to the body of knowledge on economic evaluations of mental health adherence interventions targeting YPLWH.

4.2 Implications for policy and practice

The Tanzanian government has prioritized the provision of mental support to YPWH, as evidenced by the NACP HSHSP IV and the National Training Package on

Adolescents Living with HIV and AIDS. Psychological support will improve health outcomes and the transition of YPLWH to the adult care (MoHCDGEC, 2017; MoHCDGEC, 2020). The results from this study add to the evidence of the impact of mental health adherence initiatives and underscore the need to integrate mental health support services into routine adolescent HIV care in Tanzania. Given the lack of robust results in the literature highlighted by this study, there is a need for further research funding and support to develop effective adolescent mental health care strategies and services. To this end, academic researchers must be supported to conduct high-quality research using the best available methods. The model developed in this study will facilitate decision-making and the adoption of optimal mental health adherence strategies for YPLWH in Tanzania.

4.3 Implications for further research

The model holds significant implications for further research and adds to the body of knowledge on evaluations of mental health interventions targeting YPLWH. The model can serve as a policy analysis tool following its parameterization with different mental health adherence interventions targeting the YPLWH demographic to estimate the potential long-term benefits of different strategies, facilitating their comparison and

guiding policymakers in choosing the optimal option. Furthermore, the model can be extended to include composite measures of ART adherence and non-mental-health adherence interventions in the YPLWH population or applied to other key populations. Including cost estimates, such as the cost of illness incurred by being virally unsuppressed, the model can further highlight the benefits of the strategies modeled. Lastly, the model can be used to conduct value of information analysis to determine expected gain from reducing decision uncertainty and assessing the need for further research (E. C. F. Wilson, 2015).

5. Conclusion

The current study aimed to develop a model capable of predicting the health and economic benefits of mental health HIV medication adherence interventions for YPLWH (Young People Living with HIV) in Tanzania. Using the 2016-2020 SYV pilot study, the model demonstrated that the SYV intervention led to significant improvements compared to the standard of care in Tanzania. However, it is important to note that the SYV pilot RCT was not designed to detect a treatment effect, hence, the results should be interpreted with care. Further research will be required to provide more robust results. The model offers a means to compare various mental health adherence interventions targeting YPLWH. The standardization and use of objective adherence measures in clinical studies will further aid the comparison of the multiple strategies. Given the potential for inaccuracy in self-reported adherence estimates in mental health HIV interventions among YPLWH, future studies can assess the value of additional information on objective ART adherence measures to minimize decision uncertainty.

Appendix A:

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Pg. i
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	Pg. iv
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	Pg.1
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	N/A
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Pg. 6

Setting and location	6	Provide relevant contextual information that may influence findings.	Pg. 4
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Pg. 6
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Pg. 16
Time horizon	9	State the time horizon for the study and why appropriate.	Pg. 16
Discount rate	10	Report the discount rate(s) and reason chosen.	Pg. 16
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Pg. 15
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Pg. 15
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Pg. 15
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Pg. 9
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Pg. 11
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Pg. 11

Analytics and assumptions	1 7	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Pg. 14
Characterizing heterogeneity	1 8	Describe any methods used for estimating how the results of the study vary for sub-groups.	N/A
Characterizing distributional effects	1 9	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	N/A
Characterizing uncertainty	2 0	Describe methods to characterize any sources of uncertainty in the analysis.	Pg. 17
Approach to engagement with patients and others affected by the study	2 1	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	Pg. 6
RESULTS			
Study parameters	2 2	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Pg. 17
Summary of main results	2 3	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Pg. 20
Effect of uncertainty	2 4	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the	Pg. 17

		effect of choice of discount rate and time horizon, if applicable.	
Effect of engagement with patients and others affected by the study	2 5	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Pg. 6
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	2 6	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	Pg. 18
OTHER RELEVANT INFORMATION			
Source of funding	2 7	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	N/A
Conflict of interest	2 8	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	N/A

Appendix B:

Systematic Review Search Strategy and PRISMA Flow Diagram

Table 6: Systematic review search strategy

Database: MEDLINE (searched using PubMed)

Search date: April 21, 2022

Category	Terms	Results
#1 - Youth	"young adult"[Mesh] OR "adolescent"[Mesh] OR "child"[Mesh] OR "young adult"[tiab] OR "adolescent"[tiab] OR "child"[tiab] OR "teen"[tiab] OR "juvenile"[tiab] OR "youth"[tiab]	3,945,883
#2 - HIV	"HIV"[Mesh] OR "acquired immunodeficiency syndrome"[Mesh] OR "human immunodeficiency virus"[tiab] OR "HIV"[tiab] OR "acquired immunodeficiency syndrome"[tiab]	405,471
#3 - Economic evaluations	"costs and cost analysis"[Mesh] OR "cost-benefit analysis"[Mesh] OR "cost-benefit"[tiab] OR "cost benefit"[tiab] OR "cost-effectiveness"[tiab] OR "cost effectiveness"[tiab] OR "cost-utility"[tiab] OR "cost utility"[tiab] OR "economic evaluation"[tiab] OR "economic evaluations"[tiab] OR "economic model"[tiab] OR "economic models"[tiab] OR "benefit-to-cost"[tiab] OR "cost effective"[tiab] OR "cost-effective"[tiab] OR "HIV Infections/economics"[Mesh] OR "Acquired Immunodeficiency Syndrome/economics"[Mesh]	375,377
#4 - Combining	#1 AND #2 AND #3	2,383
#5 - Narrowing	#4 NOT ("comment"[publication type] OR "case reports"[publication type] OR "editorial"[publication type] OR "letter"[publication type])	2,315

Database: Embase (searched using Elsevier)

Search data: April 21, 2022

Category	Terms	Results
#1 - Youth	'young adult'/exp OR 'adolescent'/exp OR 'child'/exp OR 'young adult':ti,ab OR 'adolescent':ti,ab OR 'child':ti,ab OR 'teen':ti,ab OR 'juvenile':ti,ab OR 'youth':ti,ab	4,670,687

#2 - HIV	'HIV'/exp OR 'acquired immunodeficiency syndrome'/exp OR 'human immunodeficiency virus':ti,ab OR 'HIV':ti,ab OR 'acquired immunodeficiency syndrome':ti,ab	551,097
#3 - Economic evaluations	'costs and cost analysis'/exp OR 'cost-benefit analysis'/exp OR 'cost-benefit':ti,ab OR 'cost benefit':ti,ab OR 'cost-effectiveness':ti,ab OR 'cost effectiveness':ti,ab OR 'cost-utility':ti,ab OR 'cost utility':ti,ab OR 'economic evaluation':ti,ab OR 'economic evaluations':ti,ab OR 'economic model':ti,ab OR 'economic models':ti,ab OR 'benefit-to-cost':ti,ab OR 'cost effective':ti,ab OR 'cost-effective':ti,ab	623,593
#4 - Combining	#1 AND #2 AND #3	2,181
#5 - Narrowing	#4 NOT ('comment':it OR 'case reports':it OR 'editorial':it OR 'letter':it)	2,143

Database: Scopus

Search date: April 24, 2022

Category	Terms	Results
#1 - Youth	TITLE-ABS("young adult") OR TITLE-ABS("adolescent") OR TITLE-ABS("child") OR TITLE-ABS("teen") OR TITLE-ABS("juvenile") OR TITLE-ABS("youth")	2,605,685
#2 - HIV	TITLE-ABS("HIV") OR TITLE-ABS("acquired immunodeficiency syndrome") OR TITLE-ABS("human immunodeficiency virus")	417,677
#3 - Economic evaluations	TITLE-ABS("cost-benefit") OR TITLE-ABS("cost benefit") OR TITLE-ABS("cost-effectiveness") OR TITLE-ABS("cost effectiveness") OR TITLE-ABS("cost-utility") OR TITLE-ABS("cost utility") OR TITLE-ABS("economic evaluation") OR TITLE-ABS("economic evaluations") OR TITLE-ABS("economic model") OR TITLE-ABS("economic models") OR TITLE-ABS("benefit-to-cost") OR TITLE-ABS("cost effective") OR TITLE-ABS("cost-effective")	441,755
#4 - Combining	#1 AND #2 AND #3	658
#5 - Narrowing	#4 AND SRCTYPE(j)	634

Database: Global Index Medicus

Search date: April 24, 2022

Category	Terms	Results
#1 - Youth	tw:(young adult) OR tw:(adolescent) OR tw:(adolescents) OR tw:(teenager) OR tw:(teenagers) OR tw:(child) OR tw:(children) OR tw:(teen) OR tw:(juvenile) OR tw:(youth)	346,633
#2 - HIV	tw:(HIV) OR tw:(human immunodeficiency virus) OR tw:(acquired immunodeficiency syndrome)	35,145
#3 - Economic evaluations	tw:(cost-benefit) OR tw:(cost benefit) OR tw:(cost-effectiveness) OR tw:(cost effectiveness) OR tw:(cost-utility) OR tw:(cost utility) OR tw:(economic evaluation) OR tw:(economic evaluations) OR tw:(economic model) OR tw:(economic models) OR tw:(cost-analysis) OR tw:(cost analysis) OR tw:(benefit-to-cost) OR tw:(cost effective) OR tw:(cost-effective)	27,182
#4 - Combining	#1 AND #2 AND #3	122

Figure 7: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

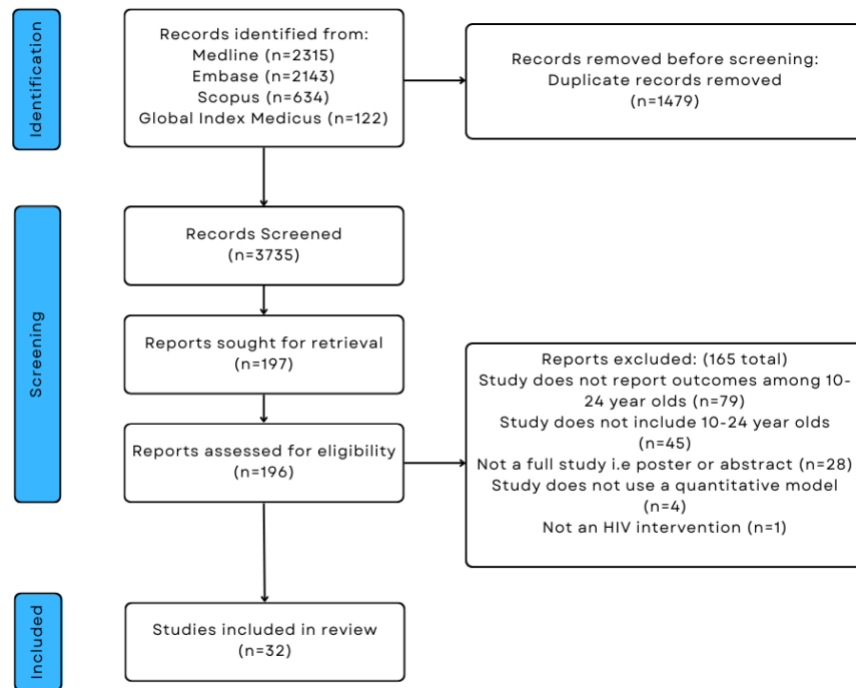


Figure 8: Showing systematic review included study reporting quality analysis–
 Legend 1=Complete fulfillment of extraction parameter, 0.5= partial fulfillment of
 extraction parameter, 0= Absence of extraction parameter. Section and study reporting
 quality included.

Section	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	Overall section reporting quality (%)	
Parameter	Bhanya	Camlin	Culture	Alstax	leKeele	Sagan	Touan	Hornales	Kahn	Wang	Awad	Kripke	Prinleb	becker	lee	2005	Bo	1998	2016	2016	2016	2016	2015	2018	2021	2020	2017	2018	2016	2021	2021	2018	2020	Overall section reporting quality (%)
1 Study objectives	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
2 Health economic analysis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6.25	
3 Study population	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
4 Setting and location	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	97.19	
5 Comparators	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
6 Perspective	1	1	1	1	1	1	1	1	1	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0.5	0.5	1	1	1	1	1	1	1	85.94	
7 Time horizon	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	93.75	
8 Discount rate	1	0	1	0.5	0	0	1	1	0.5	0.5	0.5	1	1	1	1	1	0.5	0	0	0	0	0	0	0.5	1	1	1	1	1	1	0.5	1	59.38	
9 Selection of outcomes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
10 Measurement of outcomes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
11 Valuation of outcomes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	78.13	
12 Measurement and valuation of resource and costs	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
13 Currency, price date, and conversion	1	1	1	1	1	1	1	1	1	1	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	89.06	
14 Rationale and description of model	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
15 Analytics and assumptions	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
16 Characterising homogeneity	1	0	0	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	50.00	
17 Characterising distributional effects	0	0	0	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	46.88	
18 Characterising uncertainty	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
19 Approach to engagement with patients and others affected by the study	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3.13	
20 Results - Study parameters	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
21 Results - Summary of main results	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
22 Results - Effect of uncertainty	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	96.88	
23 Results - Effect of engagement with patients and others affected by the study	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24 Discussion - Study findings, limitations, generalizability, and current knowledge	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100.00	
25 Other information - Source of funding	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	93.75
26 Other information - Conflicts of interest	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	78.13
Overall study reporting quality (%)	84.62	75.92	80.77	90.38	84.62	76.92	73.08	80.77	76.92	71.15	82.69	80.77	84.62	78.85	75.00	80.77	76.92	80.77	73.08	80.77	76.92	69.23	80.77	76.92	69.23	88.46	84.62	80.77	84.62	88.46	88.46	76.92		

Appendix C:

SYV Cost Analysis Parameters and Results

Table 7: Costing parameters.

Item	Item definition	Cost/unit	Data source
Personnel			
Trainer salary	Salary paid to individuals who trained the group leaders	\$7,060.86/FTE	RCT Key personnel interviews
Group leader salary	Salary paid to group leaders who delivered the intervention	\$3,981.28/FTE	RCT financial records
Research assistant fees	Fees paid to research assistants to conduct participant interviews and questionnaires	\$10.68/interview	RCT financial records
Phlebotomist fees	Fees paid to phlebotomists for blood sample collection	\$1.78/blood sample	RCT financial records
Site supervisor salary	Salary paid to supervisor overseeing research site	\$4,272.12/FTE	RCT Key personnel interviews
Transcription/translation fees	Fees paid to transcribe and translate documents	\$12.29/month	RCT financial records
Facilities			
Building rent for training space	Rent for facility space used to conduct group leader trainings	\$81.88/week	RCT Key personnel interviews
Building rent for intervention delivery space	Rent for facility space used to deliver the intervention	\$237.34/month	RCT financial records
Utilities			
Internet	Internet service	\$1.63/week	RCT Key personnel interviews

Phone calls	Follow-up phone calls to participants	\$3.59/participant	
Printing/office			
Writing utensils	Writing materials used to deliver the intervention	\$9.62/month	RCT financial records
SYV manuals	Manuals to facilitate group leader trainings	\$94.94/group leader	RCT Key personnel interviews
Questionnaires	Participant questionnaires	\$5.93/questionnaire	RCT Key personnel interviews
Handouts	Participant handouts	\$2.37/participant	RCT Key personnel interviews
Testing			
Viral load tests	Participant viral load tests	\$79.47/test	RCT financial records
ART adherence tests	Participant ART adherence tests	\$149.52/test	RCT financial records
Compensation			
Participant food vouchers	Food vouchers given to participants at each SYV intervention session	\$14.47/participant	RCT financial records
Participant travel vouchers	Travel vouchers given to participants at each SYV intervention session	\$30.80/participant	RCT financial records
Trainer travel allowance	Allowance given to group leader trainers for travel to training site	\$1,780/trainer	RCT financial records
Training snacks and refreshments	Meals provided to participants during group leader training	\$2.76/person	RCT Key personnel interviews
Miscellaneous			
IRB fees	Fees for annual IRB processing and renewal	\$125.01/year	RCT financial records

Table 8: Cost to deliver SYV to 58 participants in the intervention arm

Item	Total units consumed	Total cost (total units consumed x unit cost)	Per participant cost (N=58)	Per participant per year cost (N=58)
Personnel				
Trainer salary	0.077 FTE	\$543.67	\$9.37	\$9.37
Group leader salary	8.5 FTE	\$33,840.88	\$583.46	\$411.86
Research assistant fees	290 interviews	\$3,097.20	\$53.40	\$21.36
Phlebotomist fees	290 blood samples	\$516.20	\$8.90	\$3.56
Site supervisor salary	2.84 FTE	\$12,132.82	\$209.19	\$147.66
Transcription/translation fees	17 months	\$208.93	\$3.60	\$2.54
Subtotal		\$50,339.72	\$867.93	\$596.36
Facilities				
Building rent for training space	2 weeks	\$163.76	\$2.82	\$2.82
Building rent for intervention delivery space	17 months	\$4,034.78	\$69.57	\$49.10
Subtotal		\$4,198.54	\$72.39	\$51.92
Utilities				
Internet	74 weeks	\$120.62	\$2.08	\$1.47
Phone calls	58 participants	\$208.22	\$3.59	\$2.53
Subtotal		\$328.84	\$5.67	\$4.00
Printing/office				
Writing utensils	17 months	\$163.54	\$2.82	\$1.99
SYV manuals	6 group leaders	\$569.64	\$9.82	\$9.82
Questionnaires	290 questionnaires	\$1,719.70	\$29.65	\$3.93
Handouts	58 participants	\$137.46	\$2.37	\$2.37
Subtotal		\$2,590.34	\$44.66	\$18.11
Testing				
Viral load tests	290 tests	\$23,046.30	\$397.35	\$158.98
ART adherence tests	290 tests	\$43,360.80	\$747.60	\$299.04
Subtotal		\$66,407.10	\$1,144.95	\$458.02
Compensation				
Participant food vouchers	58 participants	\$839.26	\$14.47	\$10.21
Participant travel vouchers	58 participants	\$1,786.40	\$30.80	\$21.74
Trainer travel allowance	1 trainer	\$1,780.05	\$30.69	\$30.69

Training snacks and refreshments	10 days	\$160.2	\$2.72	\$0.62
Subtotal		\$4,4565.91	\$78.68	\$63.26
Miscellaneous				
IRB fees	2 years	\$250.02	\$4.31	\$2.16
Administrative fees	NA	\$10,294.44	\$177.27	\$125.29
Subtotal		\$10,544.64	\$181.58	\$127.45
Total		\$138,974.90	\$2,396.12	\$1319.11

Table 8: Cost to deliver SYV to 105 participants in intervention and control arms.

Item	Total units consumed	Total costs (total units consumed x unit cost)	Per participant costs (N=105)	Per participant per year cost (N=105)
Personnel				
Trainer salary	0.077 FTE	\$543.69	\$5.18	\$1.17
Group leader salary	20.5 FTE	\$81,616.24	\$777.30	\$175.86
Research assistant fees	525 interviews	\$5,607.00	\$53.40	\$12.08
Phlebotomist fees	525 blood samples	\$934.50	\$8.90	\$2.01
Site supervisor salary	6.84 FTE	\$29,221.30	\$278.30	\$62.96
Transcription/translation fees	41 months	\$503.89	\$4.80	\$1.09
Subtotal		\$118,426.62	\$1,127.87	\$255.17
Facilities				
Building rent for training space	2 weeks	\$163.76	\$1.56	\$0.35
Building rent for intervention delivery space	41 months	\$9,730.94	\$92.68	\$20.97
Subtotal		\$9,894.70	\$94.24	\$21.32
Utilities				
Internet	178 weeks	\$290.14	\$2.76	\$0.62
Phone calls	105 participants	\$376.95	\$3.59	\$0.81
Subtotal		\$667.09	\$6.35	\$1.44
Printing/office				
Writing utensils	41 months	\$394.42	\$3.76	\$0.85

SYV manuals	6 group leaders	\$569.64	\$5.43	\$1.23
Questionnaires	525 questionnaires	\$3,113.25	\$29.65	\$6.71
Handouts	105 participants	\$248.85	\$2.37	\$0.54
Subtotal		\$4,326.16	\$41.20	\$9.32
Testing				
Viral load tests	525 tests	\$41,721.75	\$397.35	\$89.90
ART adherence tests	525 tests	\$78,498.00	\$747.60	\$169.14
Subtotal		\$120,219.75	\$1,144.95	\$259.04
Compensation				
Participant food vouchers	105 participants	\$1,519.35	\$14.47	\$3.27
Participant travel vouchers	105 participants	\$3,234.00	\$30.80	\$6.97
Trainer travel allowance	1 trainer	\$1,780.05	\$16.95	\$3.83
Training snacks and refreshments	10 days	\$160.2	\$2.72	\$0.62
Subtotal		\$6,693.60	\$64.94	\$14.69
Miscellaneous				
IRB fees	4 years	\$500.04	\$4.76	\$1.08
Administrative fees	NA	\$20,845.42	\$198.53	\$44.92
Subtotal		\$21,345.46	\$203.29	\$45.99
Total		\$281,413.18	\$2,680.13	\$606.36

Cost analysis results

From our calculations, the total cost of the SYV program delivered to 58 participants in the intervention arm using the intent-to-treat approach was USD 138,974.90, the cost per participant amounted to USD 2,396.12, and the non-research cost per participant was USD 943.12. The total cost to deliver SYV to all participants in the RCT was USD 243,915.17, the cost per participant was USD 2,323, and the cost per participant per year was USD 701.68).

Appendix D:

Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool and Model Parameterization

Model parameterization

Probabilities

Viral suppression

To calculate the probability of viral suppression in the SYV arm over the RCT follow-up period, we determined the average proportion of virally suppressed participants in the SOC arm for each follow-up period from the RCT data using the HIV RNA threshold reported in the publication. We used the derived SOC viral suppression values to calculate the SYV viral suppression probabilities and confidence intervals from the risk ratios reported in the SYV publication using the formula below (Dow et al., 2022)–

$$\mathbf{prob\ (exposed) = RR * prob(unexposed)}$$

(prob = probability, RR = risk ratio)

ART adherence

We calculated ART adherence using participants' self-reported ART adherence and set the threshold for ART adherence to 50 and above. We determined the average proportion of participants who were ART adherent and ART non adherent based on participant viral suppression status for each follow-up time point from the RCT data. Hence, we derived separate adherence probabilities for individuals who were virally suppressed and individuals who were not virally suppressed in each study arm.

Transition probabilities between health states

For the transition between health states, we determined the number of individuals in both arms of the RCT who changed or remained in the same viral suppression status based on their viral and ART suppression status in the previous follow-up period. In the model, we input tables of the number of individuals transitioning between viral states conditioned on ART adherence as described above for each model branch (Examples of model branches are viral suppressed and adherent, viral suppressed and non adherent). The tables contained two primary columns, one for individuals making a transition, i.e., changing viral states, and another for individuals who remain in the same viral state. We then applied a beta distribution to the values in the table and set the Alpha to the event

occurring (making a transition between viral suppression states) and Beta to the nonevent (remaining in the same viral state). The beta distribution represented the rate of change. Thus, we converted the transition rates to probabilities using the ratetoprob function in TreeAgePro Healthcare. The rate to probability conversion formula is shown below -

$$\text{prob} = (1 - \text{EXP}(- \text{rate} * \text{time}))$$

(prob= probability, time = cycle length, EXP = exponent)

The probability of a transition in viral suppression between and to the same health state was conditioned on ART adherence.

Death

We calculated the probability of death in both cohorts using time-to-event analysis. We determined the effective number of participants at risk of death by subtracting the number of censored participants from the total number of participants in the cohort for each given time point. We then divided the events/deaths by the effective population at risk. The probability of death was calculated for each study follow-up timepoint. The average risk of death per cycle was applied to the model branch

corresponding to individuals who were Alive & Not virally suppressed and adherent, who transitioned and remained Alive and Not virally suppressed.

Model Validation and Verification (Using the AdViSHE checklist (Vemer et al., 2016))

Validation of the conceptual model

The conceptual model was developed following a systematic review of the literature, which sought to identify economic evaluations of mental health interventions targeting adolescents and young people living with HIV that used mathematical models. The search revealed that no nonproprietary models were available in the literature to answer the study question. Hence, we conceptualized and refined a model with input from health economists at the Duke Global Health Institute and Duke School of Medicine who have advanced training in health economics and significant research experience in health technology assessments. The experts agree that the model is appropriate for the research question/project.

Input data validation

We derived clinical inputs used in the model from patient-level data from a mental health adherence RCT pilot conducted in Moshi, Tanzania. We converted treatment effects to probabilities to fit the model. Cost data were derived from a cost analysis of the mental health adherence RCT and through targeted literature reviews to identify relevant studies published in peer-reviewed journals. Modeling experts reviewed the input data for appropriateness and noted shortcomings. Details of the statistical analysis of the mental health adherence RCT pilot can be found in published literature (Dow et al., 2022).

Validation of the computerized model

Modeling experts reviewed the computerized model developed in TreeAgePro Healthcare Version 2022. The experts have experience developing health economic models and thoroughly reviewed all model components, including the coding, formatting, and key settings. Relevant corrections were made following the feedback of the experts. Several validation exercises, including structural and internal checks and

simulations using extreme values on select parameters to detect aberrant behavior. Trace testing was conducted to identify the movement of participants in the model, and trackers were used to monitor the time spent in the viral suppression, ART adherence, and death health states. Values derived from the testing were compared to what was expected, and the model was found to behave predictably.

Operational validation

Outcomes in the model, including disability-adjusted life years, total costs, productivity, and deaths, have been reviewed and judged for appropriateness by modeling experts. However, the model has not been validated using alternative data due to a lack of access to alternative data sources. In its place, we compared the model to its data source and performed walk-throughs with clinical experts in the field to assess its appropriateness.

Table 9: Cost-effectiveness inputs with parameter distributions

Variable description	Value	Distributions and range	References
Start age of modeled cohort	18		Estimated
(current age = Start age + (_stage*0.5))			Estimated
Cost of SYV	USD 701.68	Triangular (631.51-771.85)	(Fawole et al., 2022 unpublished)
Value of statistical life year	USD 9340		(Patenaude et al., 2019)
Cost of ART support services for individuals who are alive and virally suppressed	USD 44		(Forsythe et al., 2019)
Cost of ART support services for individuals who are alive and not virally suppressed	USD 132	Triangular (88-176)	Estimated
Utility weight ART adherent & virally suppressed	0.277	Triangular (0.189-0.379)	Weights (Ackerman et al., 2022)
Utility weight ART non adherent and alive virally suppressed	0.381	Triangular (0.269-0.505)	Weights (Ackerman et al., 2022)
Probability of death in the SYV arm	0.009		Calculated using RCT data from (Dow et al., 2022)

Probability of death in the SOC arm	0.0183		Calculated using RCT data from (Dow et al., 2022)
Life expectancy of modeled cohort	72.6		(WHO, 2019)
Probability individuals in the standard of care arm are alive & virally suppressed	0.67		Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the standard of care arm who are alive & virally suppressed are ART adherent	0.698		Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the standard of care arm who are alive & not virally suppressed are ART adherent	0.723		Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the SYV arm are alive & virally suppressed	0.649 at baseline, 0.745 at six months, 0.755 at 12 months, 0.694 at 18 months and above	Triangular (0.64 - 0.66) at baseline, (0.609 - 0.891) at six months, (0.593 - 0.955) at 12 months, (0.532- 0.917) at 18 months and above	Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the SYV arm who are alive & virally suppressed are ART adherent	0.838 at baseline, 0.902 at six months, 0.769 at 12 months, 0.970 at 18 months and above		Calculated using RCT data from (Dow et al., 2022)
Probability individuals in the SYV arm who are alive & not virally suppressed are ART adherent	0.8 at baseline, 0.929 at six months, 0.769 at 12 months, 0.733 at 18 months and above		Calculated using RCT data from (Dow et al., 2022)

<p>Probability an individual in either SYV or SOC who were Alive & Not virally suppressed become Alive and Virally suppressed based on their ART adherence status</p>	<p>Beta distribution - Alpha set to event (individuals making the transition) and Beta set to non event (individuals who do not make the transition)</p>		<p>Calculated using RCT data from (Dow et al., 2022)</p>
<p>Probability an individual in either SYV or SOC who were Alive & virally suppressed become Alive & Not virally suppressed based on their ART adherence status</p>	<p>Beta distribution - Alpha set to event (individuals making the transition) and Beta set to non event (individuals who do not make the transition)</p>		<p>Calculated using RCT data from (Dow et al., 2022)</p>

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