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Cost-effectiveness of an interactive voice response system for improving retention in care and adherence to antiretroviral therapy among young adults in Uganda

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Abstract

Background New interventions aimed at increasing access to and adherence to antiretroviral therapy among young people living with the human immunodeficiency virus (YPLHIV) are needed. This study assessed the cost-effectiveness of the call-for-life interaction voice response tool compared to that of the standard of care (SOC) for promoting treatment adherence and retention in care among YPLHIV in Western Uganda.

This cost-effectiveness study used data from a randomized controlled trial and a decision-analytic Markov model to estimate the long-term outcomes and costs of the Call for Life-Interactive Voice Response (CFL-IVR) tool and the usual care from the Ugandan public payer perspective. The model was parameterized using primary data and the literature and adopted a 1-year Markov cycle. The main outcomes were mean annual costs, disability-adjusted life-years (DALYs), and the incremental cost-effectiveness ratio (ICER) in form of cost per DALY averted. The CLF-IVR was deemed cost-effective if the ICER was between 1% and 51% of Uganda's gross domestic product. We conducted deterministic and probabilistic sensitivity analyses to assess the effect of adjusting parameter values on cost-effectiveness estimates. All costs were reported in 2021 US dollars, and a discount rate of 3% was applied to both costs and outcomes.

Results The base case analysis showed that, from the Ugandan public payer perspective, the CLF-IVR led to more mean annual costs ($359 vs. $280) and averted more mean annual DALYs (15.78 vs. 11.09) than the SOC, leading to an ICER of $17 per DALY averted. The base-case results did not change significantly in the deterministic and probabilistic sensitivity analyses. The cost-effectiveness estimates were more responsive to uncertainties surrounding ART duration, viral load suppression rates, and discount rates.

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Conclusion The CLF-IVR may be a cost-effective intervention for promoting treatment adherence and retention in care among YPLHIV in Uganda and other low-income settings. Once implemented, similar interventions may lead to greater returns in encouraging adherence to ART and retention in care among YPLHIV and other vulnerable groups, and eventually favorable clinical outcomes.

Trial registration NCT04718974 Registry: clinical Trials.gov https://ichgcp.net/nl/clinical-trials-registry/NCT04718974 (20 Jan 2021).

Keywords IVR, Treatment adherence, Cost-effectiveness, YPLHIV, Retention

Background

Acquired Immune Deficiency Syndrome (AIDS) is among the leading causes of death among young people in sub-Saharan Africa [1, 2] and accounts for almost 24% of the total annual deaths [3]. Adherence to antiretroviral therapy (ART) is the principal determinant for achieving and sustaining viral suppression, which decreases the progression of AIDS and reduces the risk of mortality [4]. ART adherence and retention in care still pose a challenge to meeting the United Nations Joint HIV/AIDS Program (UNAIDS) target of 95:95:95 [5, 6]. Young people living with HIV(YPLHIV) in rural areas in low and middle-income countries (LMICs) continue to perform poorly in terms of viral load suppression, adherence to ART, and retention in care [7]. Several LMICs have low viral suppression rates, especially among young people. A study in Ghana revealed a suppression rate of 68.2% [8] and, in August 2022, the Uganda Population-Based HIV Impact Assessment survey showed 54.7% suppression in the same age group [8] and 31.2% in Nigeria [9]. Novel and innovative interventions for improving patients' adherence to ART and retention are needed across Africa. Young people are more likely to drop out of HIV care than adults, and there is a need to develop cost-effective, youth-friendly interventions to improve ART adherence and retention in care [10–12].

The Academy for Health Innovations at Infectious Diseases Institute, in conjunction with Janssen, the pharmaceutical company of Johnson & Johnson, developed a system called "Call for Life Uganda," an interactive voice response (CFL-IVR; Johnson & Johnson) technology that is based on the Mobile Technology for Community Health open-source software. IVR is an automated phone system that engages callers by combining pre-recorded messages or text-to-speech technology with a dual-tone multi-frequency (DTMF) interface, allowing clients to provide and access information via a phone without requiring a live person [13].

The CFL-IVR system offers individualized daily pill reminders, clinic visit reminders, health information tips, and remote symptom reports and management. The tool was designed to support the 3rd 95th percentile of the UNAIDS target – adherence and retention.

Is there a role for mHealth interventions in improving adherence to ART and retention in care? It certainly seems apt and possible to benchmark high mobile phone ownership and access to improve engagement and adherence to ART. A great deal of evidence indicates that mHealth interventions promoting prevention or treatment adherence for people living with HIV (PLHIV) are acceptable to adolescents and inexpensive [14] and have a positive effect on ART adherence, prevention, and treatment in PLHIV [15]. These mHealth interventions have proven effective at improving adherence to ART among other groups of PLHIV in low- and high-income settings [16–20]. The Call-for-life study showed that participants randomized to receive mHealth (CFL-IVR) were retained in care, had improved adherence and a greater percentage of viral suppression than did those in the standard of care (SOC) [21] and were willing to pay and continue with the intervention [22].

Despite the evidence of the positive effect of mHealth on health outcomes, there has been slow progress in implementing these interventions. Economic evaluation studies, particularly cost-effectiveness analyses, are instrumental in influencing the ability of governments and other decision-makers to prioritize and implement mHealth interventions [23, 24]. Notably, a few HIV-related mHealth interventions were found to be cost-effective in LMICs [25–27]. Despite the clinical efficacy of CLF-IVR in terms of its ability to suppress the viral load [21], there is a need for evidence of its economic efficiency (value for money) before it can be scaled up. Therefore, this study evaluated the cost-effectiveness of the CLF-IVR compared to the SOC in promoting treatment adherence and retention in care among adolescents living with HIV in Western Uganda.

Methods

This was a cost-effectiveness study, aimed to determine the incremental cost-effectiveness ratio (ICER) in form of cost per disability-adjusted life year (DALY) averted following the use of the CLF-IVR compared to the SOC. Following the HIV epidemiology data in Uganda, this incremental analysis was conducted using a decision-analytic Markov model from the Ugandan public payer perspective, as recommended by the standard health economic evaluation reporting guidelines [28, 29].

The main outcomes were mean annual costs and DALYs averted, and the ICER in the form of cost per DALY averted. All costs and outcomes were discounted at an annual rate of 3%, and a lifetime horizon (i.e., a young adult living with HIV was followed up until death) was adopted. The interventions considered in this study followed a recent randomized controlled trial (RCT) in which 206 young adults living with HIV in Kiryandongo district, Western Uganda, were randomized to receive either the CLF-IVR or SOC [21, 30]. Each arm had 103 participants who were seen at baseline, followed up at 6 months, and 12 months from 12th August 2020 to 1st June 2022.

The new intervention (CLF-IVR) was an interactive voice call reminder for daily pills, appointment visit reminders, and weekly educational health messages; the participants interacted with the systems through a dial pad following voice prompts. These messages were received as voice calls to the personal mobile phones of those on the intervention arm at pre-scheduled times at the study sites [21]. In contrast, the comparator was the SOC, which was based on the Ministry of Health 2018 Consolidated Guidelines for the Prevention and Treatment of HIV, including services that foster adherence among clients to ART to achieve viral suppression through facility-based ART adherence, education, and counseling. The SOC is supposed to offer clinic-based follow-up, including phone calls by lay counselors to remind patients about appointments, tracking and follow-up of those who do not keep appointments, including a loss to follow-up/transfers, psychosocial support, counseling, and linkage to support services.

Structure of the model

This Markov model simulated the health outcomes (DALYs) and costs for a young adult living with HIV over a lifetime following the use of the CLF-IVR and a Markov cycle of one year, similar to HIV epidemiology. An 18-year-old young adult who has been using the CLF-IVR intervention, is retained in care and adhering to the ART guidelines, moves through three Markov states—the HIV state, AIDS state, and death state (Fig. 1). This study did not consider different tunnel states based on the CD4-cell count since these data were unavailable. As such, we used viral load suppression rates of 74% and 52% in the CLF-IVR and SOC arms, respectively [21].

Transition probabilities and outcomes

Table 1 shows the probabilities (and other variables) used to parameterize the Markov model. These parameters are based on the primary study, HIV epidemiological data from Uganda, and the published literature. A study by Gurprit et al., estimated the transition probabilities of progressing across WHO HIV stages – stages 1, 2,3,4, and 5—among patients on ART in India at year 1 and year 5 [31]. Given that our study used a 3-state Markov model, the HIV state comprised stages 1, 2, and 3, while the AIDS state is stage 4 from *Gurprit* et al., and in the study, a patient in state 1 had a 67% likelihood of remaining in the same condition after a year, compared to 19% and 4% for moving to state 2 and dying, respectively. In the same study, a patient in state 2 had a 33% probability of remaining in the same state after one year, a 38% risk of moving to state 1, and a 23% chance of moving to state 3 after one year, while a patient in state 4 had a 30% likelihood of remaining in the same condition after a year and a 41% risk of returning to state 3, these one-year transition probabilities from stages 1, 2 and 3 to stage 4 from the India study, were used to estimate the one-year transition probability from the HIV state to the AIDS state in our study [32]. Other transition probabilities were obtained from a study in China [33]. In addition, we used the World Health Organization (WHO)'s life tables to estimate background mortality, i.e., death that is not related to HIV or AIDS [34].

We conservatively assumed that the HIV state would take an initial distribution of 100% in the first cycle, i.e., all participants started in the HIV state in the first cycle before being distributed to other states in subsequent cycles. DALYs can be calculated by summing the years of life lost and lived in disability due to HIV [35]. The years of life lost (YLLs) were estimated as the probability of death multiplied by the life expectancy of 64 years in Uganda [36]. In contrast, the years of life lived in disability (YLDs) were estimated as the probability of being in the HIV and AIDS states multiplied by the

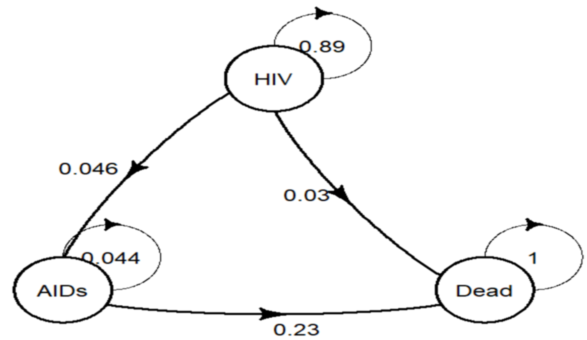

Fig. 1 A schematic structure of the Markov model. There are three Markov states, one can transition from HIV to either AIDS or death. Whereas the person with AIDS can only move to death

Table 1 Parameter values used to assess the cost-effectiveness of the CLF-IVR compared to the SOC in Uganda

Input parameters	Base case value	Sensitivity range[a]	Reference
Initial distribution			
HIV	1.00	0.8—1.2	Assumption
AIDS	0.00	0	Assumption
Death	0.00	0	Assumption
Transition probabilities, %			
HIV state to AIDS state	0.046	0.02—0.08	[32]
HIV state-to-death state	0.03	0.0063—0.082	[33]
AIDS state-to-death state	0.23	0.16—0.33	[33]
Effect of intervention			
Viral load suppression rate, %			
VL suppression rate –IVR	0.74	0.68—0.79	Primary study
VL suppression rate –SOC	0.52	0.45—0.58	Primary study
DALY weights			
DALY weight—HIV with ART	0.27	0.18—0.38	[38]
DALY weight—AIDS with ART	0.08	0.05—0.11	[38]
Mean life expectancy at birth in Uganda (years)			
Life expectancy at birth in Uganda	64	51—78	[36]
Discount rate, %			
Discount rate	0.03	0.01—0.06	[29]
Costs, US $			
Annual operation cost –CLF-IVR	36	29—43	Primary study
ART duration in years over a lifetime –IVR	486	389—583	Assumption
ART duration in years over a lifetime – SOC	898	718—1078	Assumption
Annual cost of ART for a young adult living with HIV	369	295—443	[39]

Abbreviations: *ART* Antiretroviral therapy, *CLF-IVR* Call for life interactive voice response, *DALY* Disability-adjusted life year, *SOC* Standard of care, *VL* Viral load

[a] Sensitivity ranges are based on the 95% confidence intervals and ± 20% for costs and life expectancy

respective DALY weights for a person enrolled on ART, as reported in the Global Burden of Disease Study [37].

Determination of costs and resources

The full costs of implementing the CLF-IVR were directly obtained from the financial records at the Infectious Diseases Institute (IDI) during the implementation period. Since this study was conducted from the Ugandan public payer perspective, the appropriate costs were identified, measured, and valued [40]. The Ugandan public payer perspective – theoretically similar to Uganda's Ministry of Health – included direct medical and nonmedical costs and excluded all indirect costs, such as patient lost time and out-of-pocket expenses [41]. The costs of treating, supporting, and caring for a young adult living with HIV and the transport and lost productivity (sickness) costs were obtained from a study by *Moreland* et al*.* [39] and adjusted to the median time spent on ART per arm, as reported in the study by Naggirinya et al. [22]. The costs of running the CLF-IVR included capital costs, such as computers and cell phones, annualized at a 3% discount rate to account for depreciation, data connection and telephone charges, materials and production, adherence calls, software development support, and creation of IVR voice files. All costs from the literature were inflated and reported in 2021 US dollars.

Assessment of uncertainty

We used deterministic sensitivity analyses to assess the effect of changing model parameter values on cost-effectiveness estimates. Given the unavailability of 95% confidence intervals for cost parameters, we used a ± 20% change and a normal distribution. We used the lower and upper limits of the 95% confidence intervals for probability parameters to estimate standard errors and assigned a beta distribution. These ranges were used in the one-way (deterministic) sensitivity analysis, presented as a tornado diagram. Through Monte Carlo simulation of 1000 iterations, we plotted a cost-effectiveness plane and examined the quadrant where the largest proportion of pairs of incremental costs (vertical axis) and incremental DALYs (horizontal axis) lie to ascertain whether the CLF-IVR would be an efficient strategy. The CLF-IVR was deemed cost-effective if the ICER was between 1%

Table 2 Base case analysis results comparing the CLF-IVR to the SOC in Uganda

	Payer Perspective		
	CLF-IVR	**SOC**	**Incremental**
Base-case (undiscounted)			
Mean annual costs	499	369	130
Mean annual DALYs	33.92	23.83	10.08
ICER ($/DALYs)			13
Base-case (discounted at 3%)			
Mean annual costs	359	280	80
Mean annual DALYs	15.78	11.09	4.69
ICER ($/DALYs)			17

CLF-IVR Call for life interactive voice record system, *DALYs* Disability-adjusted life-years, *ICER* Incremental cost-effectiveness ratio, *SOC* Standard of care

and 51% of Uganda's per capita gross domestic product (GDP) of $884 [42], as suggested by Woods et al. [43]. All the cost-effectiveness analyses were conducted in Microsoft Excel. This study followed the consolidated Health Economic Evaluation Reporting Standards (CHEERs) statement, developed to enhance economic evaluation for decision-making [28].

Results

Table 2 shows the mean annual costs and DALYs averted for a young adult living with HIV who has access to either the CLF-IVR or the SOC. From the Ugandan public payer perspective, the CLF-IVR led to more mean annual costs ($359 vs. $280) and averted more mean annual DALYs (15.78 vs. 11.09) than the SOC, leading to an ICER of $17 per DALY being averted.

Deterministic sensitivity analysis indicated that the ICER was most responsive to the duration of ART (both arms), discount rate, and viral load suppression rate (both arms) (Fig. 2).

Changes in these parameters do not lead to significant variation from the base case results; i.e., the ICERs are still within the acceptable willingness-to-pay threshold of 1% to 51% of Uganda's GDP per capita.

The cost-effectiveness plane shows the uncertainty surrounding the incremental costs and DALYs averted (Fig. 3).

The Monte Carlo iterations comparing the CLF-IVR to the SOC lie below and above zero, showing that there is great certainty that the CLF-IVR is costlier than the SOC but can also be less costly. In other words, the largest proportion of pairs of incremental costs against the incremental DALYs lying in the northeast quadrant of the cost-effectiveness plane shows that the CLF-IVR is costly but more effective than the SOC. The dispersed pairs in the southeast quadrant indicate that the CLF-IVR is less costly and more effective than the SOC, i.e., it can lead to cost savings and favorable health outcomes.

Discussion

The elimination of HIV will largely depend on a plethora of interventions that target key hard-to-reach populations, particularly adolescents and young adults. These

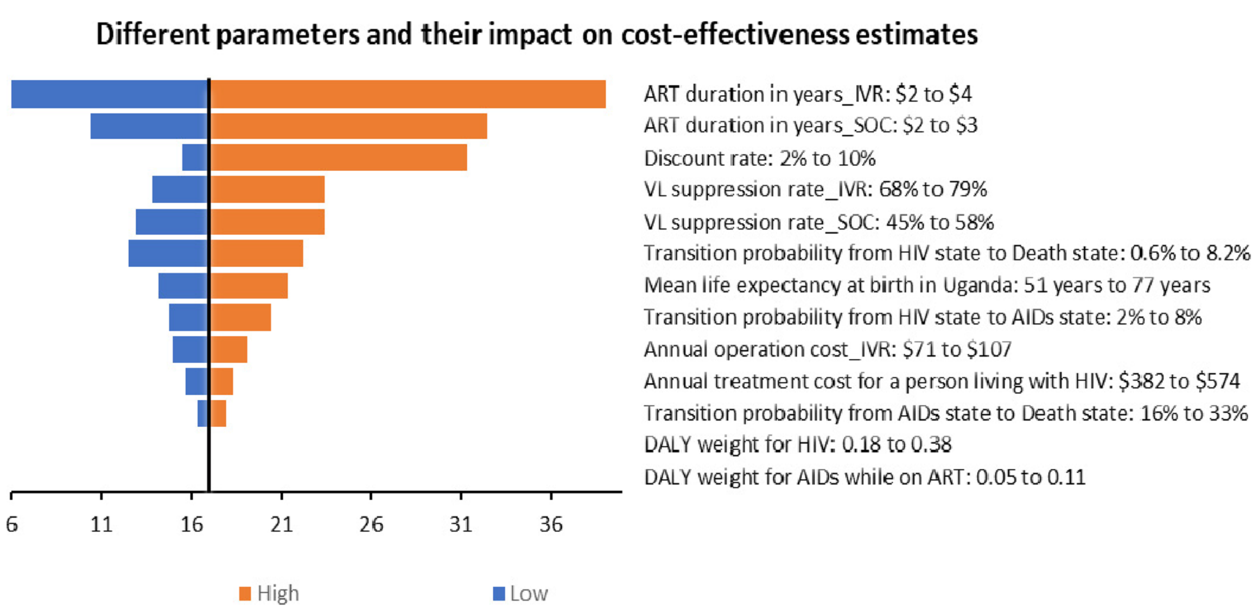

Fig. 2 Tornado diagram from the deterministic sensitivity analysis. ART, antiretroviral therapy; DALY, disability-adjusted life year; IVR, interactive voice record; VL, viral load

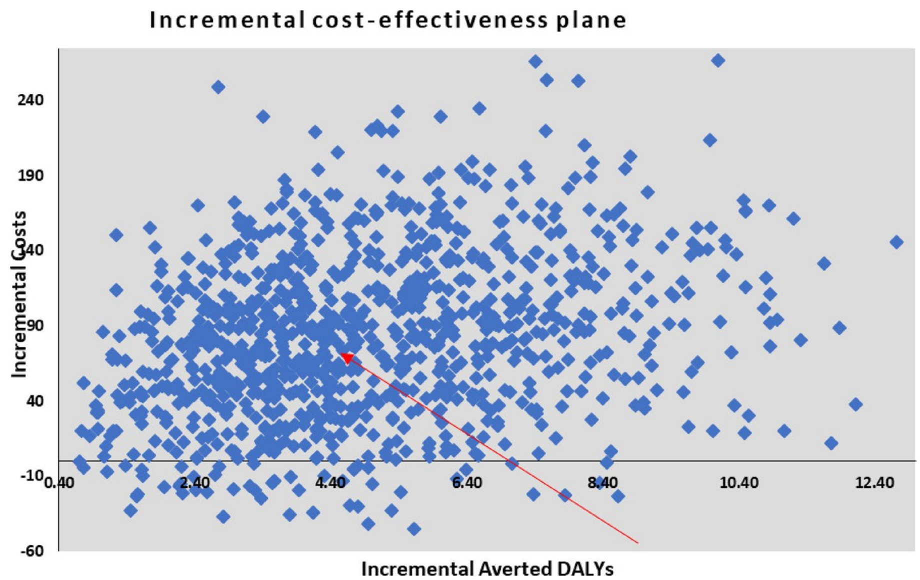

Fig. 3 A scatter plot from Monte Carlo simulation for incremental costs-effectiveness plane, the arrow shows the base case incremental costs and DALYs averted

interventions must promote adherence to ART and retention in care among these risky but well-exposed populations since most have access to the Internet and mobile phones [44–47] [48]. Using data from an RCT, we assessed the cost-effectiveness of the CLF-IVR compared to the SOC in promoting treatment adherence among adolescents living with HIV in Western Uganda. Although the CFL-IVR led to a statistically significant decrease in VL because it promoted adherence to ART and retention of care [21, 22, 30], the current cost-effectiveness study extends beyond clinical effectiveness and includes intervention costs and composite outcomes, such as DALYs. The incremental cost-effectiveness analysis was conducted on the new intervention "CLF-IVR" in comparison with the SOC "care as usual where a young adult visits the facility without any automated scheduled reminders" from the Ugandan public payer perspective, as recommended by the CHEERS statement [28] and the second panel on cost-effectiveness in health and medicine [29]. It is worth noting that a decision-analytic Markov model was used for this comparative analysis over a lifetime horizon. This model estimated DALYs as health outcomes and costs for both the CLF-IVR and SOC and all costs from the literature were adjusted to 2021 US dollars using Uganda's consumer price indices [49].

The results from the incremental cost-effectiveness analysis show that the CLF-IVR was more cost-effective than the SOC from the Ugandan public payer perspective. The ICER per DALY averted was $17, and the new intervention was deemed cost-effective if the ICER was between 1% and 51% of the country's GDP per capita [43]. Given Uganda's GDP per capita of $884 in 2021 [42], the ICER of $17 from our study is perfectly within the set threshold. These results agree with other economic evaluation studies in different settings that suggest that mHealth interventions for improving adherence to ART are affordable and cost-saving and may even become cheaper due to low marginal costs if scaled up to large groups of participants [25–27, 50].

Our results were robust to deterministic and probabilistic sensitivity analyses; i.e., the cost-effectiveness estimates did not significantly change after adjusting individual model parameters. The cost-effectiveness estimates were most responsive to the uncertainty surrounding the duration of ART, the percentage of patients with viral load suppression in either arm, and the discount rate. For instance, an increase in the duration of ART from two to four years would lead to an increase in incremental costs from $28 to $183, leading to an increase in the ICER from $6 to $39 per DALY averted – though still within the acceptable willingness-to-pay threshold of 1% to 51% of Uganda's GDP per capita [43]. With the increase in the viral load suppression rate from 68% to 79%, the incremental costs remain constant as incremental DALYs significantly increase, leading to a reduction in the ICER per DALY averted from $23 to $14. This means that an increase in the viral load suppression rate may, in the long run, lead to cost savings—ICERs continue to decrease significantly—as shown by the distribution of pairs of incremental costs and DALYs in the southeast quadrant of the cost-effectiveness plane.

Our study results should be interpreted cautiously; a person living with HIV may visit tunnel states—a series of temporary Markov states in a fixed sequence—based on the CD4 + cell count before progressing to the advanced HIV (AIDS) state. These tunnel states represent different utilities and costs and were replaced with one Markov state, "HIV state," since this is clinically acceptable, as seen in other HIV-related studies elsewhere [33] [51]. This assumption was necessary to account for the lack of data on CD4 + T-cell counts within the primary study population.

Given that the clinical effectiveness parameters were obtained from an RCT, our study avoided residual selection bias, as reported in other HIV-related studies in low-income countries [41]. It is also worth noting that this study used a decision-analytic model to extrapolate surrogate "intermediate" outcomes to long-term composite outcomes (DALYs) using a lifetime horizon from the viewpoint of the Ugandan public payer. These results are generalizable to Sub-Saharan Africa and most LMICs, where HIV prevalence is high and the largest population is young. The CFL-IVR is scalable to different case uses in chronic care like diabetes, hypertension, and tuberculosis.

Conclusion

Our study demonstrated that the CLF-IVR is cost-effective and may be an efficient strategy for promoting treatment adherence among adolescents living with HIV in Uganda and other low -and middle-income settings. Moreover, this study provides economic evidence for the implementation of the CFL-IVR and similar interventions among YPLHIV who are struggling with viral suppression to support ART adherence and retention in care. We believe this research provides essential insights for policymakers and healthcare providers aiming to enhance retention in care and treatment adherence through innovative mHealth solutions.

Abbreviations

ART	Antiretroviral therapy
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CLF-IVR	Call-for-life– Interactive Voice Response
CPHL	Central Public Health Laboratories
GDP	Gross Domestic Product
ICER	Incremental Cost-effectiveness Ratio
LMICs	Low- and Middle-Income countries
PLHIV	People Living with HIV
RCT	Randomized Controlled Trial
SOC	Standard of Care
VL	Viral Load
YPLHIV	Young People Living with HIV

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Authors' contributions

ABN and EN conceived the study, analysed the data, and wrote the first draft of the manuscript. MSN(RIP) analysed the effectiveness trial data and contributed substantively to the initial draft. FM and AN provided the CFL-IVR system data, and analysed the system call data. PW, JR, DBM and RPR contributed to the conception, supervision of doctoral study, design of the study and critical revision of the initial draft.RJ and MD contributed to the conception, supervision of the doctoral study, design of the study, and critical revision of the manuscript. RPR contributed to the funding of the project. All the authors revised and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to partcipate

This study was approved by the Makerere University School of Medicine Higher Degrees Research Ethics Committee (REC Ref 2019–083) and the Uganda National Council of Science and Technology (Ref HS 576ES). All participants gave written informed consent.

Consent for Publication

N/A.

Competing interests

RPR discloses that Infectious Diseases Institute received research funding from Janssen, the Pharmaceutical Companies of Johnson and Johnson for work on Call for Life and other research projects. Other authors report no competing interests.

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