Effect of Text Messaging Plus Peer Navigation on Viral Suppression Among Youth With HIV in the iCARE Nigeria Pilot Study

Babafemi O. Taiwo, MBBS, FAS,[a] Kehinde M. Kuti, MBBS, MSCI,[b] Lisa M. Kuhns, PhD, MPH,[c,d] Olayinka Omigbodun, MBBS, MPH, FAS,[e,f] Olutosin Awolude, MBBS, MSc,[b,g] Adedotun Adetunji, MBChB, MSCI,[h] Baiba Berzins, MPH,[a] Patrick Janulis, PhD,[i] Amy K. Johnson, PhD, MPH,[c,d] Ogochukwu Okonkwor, MPH,[a] Bibilola D. Oladeji, MBBS, MSc,[i] Abigail Muldoon, MS,[d] Olubusuyi M. Adewumi, PhD,[j] Paul Amoo, MPH,[b] Hannah Atunde, MPH,[b] Bill Kapogiannis, MD,[k] and Robert Garofalo, MD, MPH[c,d]

Background: Consistent with the global trend, youth with HIV (YWH) in Nigeria have high rates of viral nonsuppression. Hence, novel interventions are needed.

Setting: Infectious Diseases Institute, College of Medicine, University of Ibadan, Nigeria.

Methods: In a single-arm trial, participants aged 15–24 years received 48 weeks of a combination intervention, comprising daily 2-way text message medication reminders plus peer navigation. The primary outcome measure was viral suppression less than 200 copies/mL. The secondary outcome measures included self-reported adherence on a visual analog scale and medication possession ratio, each dichotomized as ≥90% (good) or <90% (poor) adherence. The outcomes were analyzed using McNemar test. Retention in care, intervention feasibility and acceptability, and participants' satisfaction were also assessed.

Results: Forty YWH (50% male participants) were enrolled: mean age 19.9 years (SD = 2.5), 55% perinatally infected, and 35% virologically suppressed at baseline. Compared with baseline, the odds of virologic suppression was higher at 24 weeks (odds ratio = 14.00, $P < 0.001$) and 48 weeks (odds ratio = 6.00, $P = 0.013$). Self-reported adherence (≥90%) increased from baseline at 24 weeks (63%, $P = 0.008$) and 48 weeks (68%, $P = 0.031$). Medication possession ratio ≥90% increased at weeks 24 and 48 (85% and 80%, respectively), achieving statistical significance at 24 weeks alone ($P = 0.022$). Retention in care at 48 weeks was 87.5%. All (37/37) participants at week 48 were fully or mostly satisfied with the intervention.

Conclusion: Daily 2-way text message reminders plus peer navigation is a promising combination intervention to improve viral suppression among YWH in Nigeria.

Key Words: viral suppression, youth, phones, peers, adherence

(*J Acquir Immune Defic Syndr* 2021;87:1086–1092)

INTRODUCTION

Since 2016, guidelines in Nigeria, Africa's most populous country, have recommended antiretroviral treatment (ART) regardless of CD4 cell count for all people with HIV.[1] Suppression of HIV-1 viremia curbs AIDS-related morbidity and mortality, limits viral transmission, and is essential to end the epidemic.[2–4] Consistent with the global trend, youth (15–24 years of age) in Nigeria have not benefited from ART as much as adults.[5–8] In 2017, fewer than half of youth with HIV (YWH) receiving care at the Infectious Disease Institute,

Received for publication November 24, 2020; accepted March 17, 2021.

From the [a]Division of Infectious Diseases and Center for Global Health, Northwestern University, Chicago, IL; [b]Infectious Disease Institute, College of Medicine, University of Ibadan, Nigeria; [c]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL; [d]Division of Adolescent Medicine, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [e]Department of Child and Adolescent Psychiatry, and Centre for Child and Adolescent Mental Health, College of Medicine, University of Ibadan, Nigeria; [f]Department of Psychiatry, College of Medicine, University of Ibadan, Nigeria; [g]Department of Obstetrics and Gynecology, and Infectious Disease Institute, College of Medicine, University of Ibadan, Nigeria; [h]Department of Family Medicine, University College Hospital, Ibadan, Nigeria; [i]Department of Medical Social Sciences, Northwestern University, Chicago, IL; [j]Department of Virology, College of Medicine, University of Ibadan, Nigeria; and [k]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD.

Research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under Award Number UG3HD096920. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Research reported in this publication was also supported by the Fogarty International Center of the National Institutes of Health under Award Number D43TW009608 and by the National Institutes of Health's National Center for Advancing Translational Sciences, Grant Number UL1TR001422. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Babafemi O. Taiwo, MBBS, FAS, Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, 645 N Michigan Avenue, Suite 900, Chicago, IL 60611 (e-mail: b-taiwo@northwestern.edu).

College of Medicine, University of Ibadan, (IDI/CoMUI), Ibadan, Nigeria, were virologically suppressed (unpublished data). Evidence-based interventions are needed to optimize ART outcomes in YWH.[9]

Mobile phones are powerful tools for ART-related interventions,[10,11] and there were more than 190 million active mobile phone subscriptions in Nigeria in April 2020.[12] The widespread preference for text messaging among youth makes it uniquely promising for youth-directed interventions. In 2016, the US Centers for Disease Control (CDC) endorsed an innovative 2-way text message reminder intervention (TXTXT) for promoting ART adherence in YWH.[13] This endorsement was based on a study by Garofalo et al[14] in which 16- to 29-year-old patients who received the TXTXT were more than twice as likely to report >90% adherence to ART over the 6-month intervention period, and the improvements were sustained at 6 months postintervention. TXTXT has not been evaluated outside the United States.

Engagement of peers is another potential way to improve ART outcomes in youth, particularly adolescents (10–19 years of age), because peer influences on health and well-being are greatest during this stage of life.[15–18] Indeed, peer navigation and support are recommended by the World Health Organization[19] (WHO) as an evidence-based approach to improve ART outcomes in youth across the HIV care continuum. Peer support ranks high among potential facilitators of ART adherence among YWH in sub-Saharan Africa,[20,21] which harbored 78% of the global population of YWH in 2017.[22]

Studies of interventions to improve ART outcomes among 15- to 24-year-old patients in sub-Saharan Africa have failed to demonstrate improvement in ART adherence and loss to follow-up, even when the same interventions were effective in older individuals.[23–25] Although these results can reflect challenges in addressing the unique struggles of youth, they may also indicate the limitations of single interventions in addressing complex multidimensional determinants of ART success. Combination interventions may be more effective than single interventions,[26] but this is not a consistent finding.[27]

The Intensive Combination Approach to Rollback the Epidemic in Nigerian Adolescents Study (iCARE Nigeria) is a 2-phase trial with HIV testing and treatment intervention arms, each incorporating mobile health (mHealth) technology and peer navigation. The iCARE Nigeria was adapted for Nigerian youth through broad input from local YWH and other stakeholders.[28] In this study, we report the findings of the first (pilot) phase of the treatment intervention arm of the iCARE study, where we hypothesized that the investigational combination intervention will improve the odds of viral suppression among YWH aged 15–24 years at IDI/CoMUI. We also tested, as secondary outcomes, the effects of the combination intervention on adherence and retention in care, intervention feasibility and acceptability, and participants' satisfaction.

METHODS

Setting

This study was conducted at IDI/CoMUI, which receives support from the CDC-funded AIDS Prevention Initiative in Nigeria (APIN) Public Health Initiatives and provides ART to more than 6000 persons with HIV, aged 14 years or older. Antiretroviral drugs are dispensed through an on-site pharmacy, and routine viral load and CD4 cell monitoring are also provided at no cost to YWH. Youth with viral load >1000 copies/mL after at least 6 months of ART receive enhanced adherence counseling. Those with persistent viremia despite 3 months of enhanced adherence counseling are evaluated for an empiric switch to second- or third-line ART regimens. A YWH youth club meets on-site every other month for peer interaction, support, and education.

Study Design

A collaborative working group of community and governmental stakeholders and 2 YWH focus groups were conducted in December 2018 in Ibadan, Nigeria, to adapt the combination peer navigation and text message reminder intervention to the local context. Findings from this formative research suggested that the combination intervention should include low navigator-to-peer ratio (1:5) and volunteer-based navigators to promote sustainability and altruism and flexible matching of navigator to peer and low requirements for mobile phone data use to promote engagement. With the findings from this formative research,[28] we designed a locally adapted combination intervention consisting of daily, 2-way, personalized text message medication reminders (TXTXT) plus peer navigation and then conducted a single-arm study of its effect on viral suppression and other HIV care continuum outcomes over 48 weeks.

Study Participants

To be considered eligible, the potential participant had to be in the age range of 15–24 years, HIV-seropositive, a registered patient at IDI/CoMUI, on ART for at least 3 months, able to understand and read basic English and/or Yoruba, able to provide consent, and in the intention to remain a patient at IDI/CoMUI during the 48-week follow-up period. In compliance with the 2014 Nigeria Federal Ministry of Health Guidelines, minors aged 16 or 17 years, or aged 15 years and emancipated, provided consent for themselves without parental involvement.[29]

Recruitment Procedures

To recruit participants, we created a sampling frame of potentially eligible youth from medical records at IDI/CoMUI and stratified into virologically suppressed (HIV-1 RNA <200 copies/mL) or viremic (≥200 copies/mL) group. A random sample was then selected as every "nth" YWH based on the ratio of target sample size to the number of YWH in the sampling frame. Enrollment was monitored to ensure that not more than 35% of selected individuals were virologically suppressed to reflect the clinic's proportion of virologically suppressed youth. Youth selected from the sampling frame were approached by study staff to determine their interest in and eligibility for the study. As needed, based on refusals or no-shows, the sampling frame was

reconstituted as a ratio of the remaining sample needed to the remaining YWH in the sampling frame. These procedures were followed until the accrual target of 40 was reached.

Text Message Reminders

YWH worked with study staff to develop the text message library and ensured it contained expressions understood and commonly used by youth. The text messages, which were designed to promote ART adherence, were delivered through the Dimagi Commcare platform (https://www.dimagi.com/commcare/). Participants used their own phones for text messaging; however, a phone was provided to those without one. The daily text messages included a personalized initial medication reminder that coincided with the individual's chosen time for antiretroviral drug ingestion. This was followed by a second message 15 minutes later, asking whether they took their medication, with a request for reply (yes or no). An encouraging automated message (based on the message library) was then triggered by their reply. Both the initial and follow-up messages were chosen by each youth and personalized to reflect content meaningful to them. To protect confidentiality, messages were worded in a way that would not reveal the participant's HIV status if read by a third party (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B656).

Peer Navigation

Peer navigators were selected from the IDI/CoMUI clinic. Requirements for this role included being virologically suppressed in the previous 12-month period (if available), aged 18–30 years, and clinically stable, according to their physician's subjective assessment. The peer navigators received didactic lectures and practicums over the course of 2 weeks, delivered by the study investigators and staff supervisors, covering general professionalism, privacy and confidentiality, basic HIV education, human rights and protections, mental health, self-care, and roles and responsibilities of peer navigators (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B656). In line with the findings from formative YWH focus groups, we matched each peer navigator to 4 or 5 study participants based on salient shared characteristics, including sex, age, residence location, and religion.[28] We allowed older ages for peer navigators than participants.[28] After assessment of the participant's needs and development of an action plan by clinic staff, peer navigators made at least one contact (in-person or phone) every 2 weeks with participants to support goals of the action plan. Peer navigators also collaborated with clinic staff to facilitate referrals to mental health and other services, accompanied participants to appointments as needed, and provided general peer support (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B656). In addition, based on formative research, peer navigators were considered volunteers to promote altruistic motivations and enhance sustainability. Accordingly, they received nominal stipends, primarily to cover transportation and communication expenses.

Ethics

Institutional Review Board approval was obtained from Northwestern University, Lurie Children's Hospital, and the joint University of Ibadan/University College Hospital Ethics Committee.

Data Collection and Outcomes Measures

Data were collected for this study through interviewer-administered electronic questionnaires, medical records abstraction, and blood specimen collection at baseline and at 24 and 48 weeks postbaseline. Collected demographic characteristics included age, sex, ethnic group, highest level of education, religion, and phone ownership or access. Medical history abstracted from records included mode of infection, current ART regimen, and drug pick-up information from 24 weeks before baseline through 48 weeks on study. Each participant was asked to provide approximately 100 strands of hair at baseline, week 24, and week 48 to measure antiretroviral drug levels.

The primary study outcome was viral suppression, defined as viral load <200 copies/mL. Viral load quantification occurred at an HIV Reference Laboratory, using real-time HIV-1 COBAS assay (Roche Molecular Systems, Inc., Pleasanton, CA) with a lower detection limit of 20 copies/mL.

The secondary outcomes included medication adherence and retention in HIV care. The adherence measures were as follows: (1) self-reported 30-day adherence on a visual analog scale (VAS) of 0–100,[30] (2) drug pick-up adherence based on medication possession ratio (MPR) calculated from pharmacy records,[31–33] and (3) antiretroviral drug levels in hair.[34] MPR was calculated, using drug pick-up records over the 24-week period preceding the evaluation date, as the total number of days' supply obtained, including the last fill, divided by the number of days between the first fill and the last day of the observation window (also known as continuous multiple-interval measures of medication availability).[35] Values greater than 100% were truncated to 100%. We evaluated adherence to the regimen rather than individual drugs because the antiretroviral drugs in each participant's regimen were always dispensed together. Both VAS and MPR values were created into dichotomous indicators of ≥90% adherence (good) or <90% adherence (poor).[36]

Retention in care was defined as 2 HIV care–related visits to IDI/CoMUI in each 24-week observation period. We also assessed intervention feasibility, acceptability, and satisfaction using a modified version of the client satisfaction questionnaire (CSQ-8).[37] Feasibility was measured by the ratio of assigned peer navigator to participants compared with the planned ratio of 1:5 and number of navigator–participant encounters compared with plan of one in every 2 weeks. Acceptability and satisfaction were measured at 48 weeks by assessing whether the intervention activities were delivered to the participant as they expected, were intrusive or bothersome, and met expectations for privacy. Overall satisfaction with the intervention was assessed as well.

Data Analyses

Changes between preintervention and postintervention periods were compared using McNemar test. We used an intent-to-treat approach for the primary analysis; therefore, participants who were deceased or lost to follow-up were coded as not suppressed. We prespecified that the combination intervention would be considered clinically significant and merit further investigation if we observed a greater than 30% increase from baseline in the proportion of youth with viral load <200 copies/mL after 48 weeks of the intervention, estimated to correspond to an odds ratio (OR) of ≥1.5. For descriptive statistics, percentages were calculated for dichotomous outcomes and mean values for continuous outcomes.

RESULTS

Participant Characteristics

A total of 46 YWH were selected from the sampling frame of whom 5 refused to participate and 1 was ineligible. The 40 participants (20 male participants) enrolled (Table 1) had a mean age of 19.9 years (SD = 2.5, range =15–24). At baseline, 36 participants (65%) owned or had access to a cell phone to receive the intervention; the study provided phones to the remaining 14 participants; 3 additional phones were distributed to replace lost or malfunctioning personal (n = 2) or study-provided (n = 1) phones. All participants completed the week 24 visit, whereas 37 completed 48 weeks (1 died and 2 lost to follow-up).

Virologic Outcomes

The proportion of YWH with viral suppression was 35% at baseline and 68% at 24 weeks, an increase of 94%. At 48 weeks, 60% was suppressed, an increase of 71% from baseline. Viral suppression rates overall and in subgroups are tabulated in Table 2. Compared with baseline, the odds of being virologically suppressed were substantially higher at 24 weeks (OR = 14.00, $P < 0.001$) and at 48 weeks (OR = 6.00, $P = 0.013$) of the combination intervention.

Increases in viral suppression rates were seen across subgroups: male versus female participants; perinatally infected versus nonperinatally infected participants; first-line versus second-line regimens; and owned/had access to cell phone or not at baseline. Transition from suppressed to viremic status was rare; of the 16 participants who were not virologically suppressed or were deceased or lost to follow-up at week 48, only 2 were suppressed at baseline.

Adherence and Retention in Care

Self-reported ART adherence ≥90%, based on VAS, was 43% at baseline. This increased from baseline levels to 63% ($P = 0.008$) at 24 weeks and 68% ($P = 0.031$) at 48 weeks. Self-reported adherence was not significantly correlated with viral suppression at 24 (r = 0.014, $P = 0.933$) or 48 weeks (r = 0.305, $P = 0.056$).

MPR indicated that 63% of participants had ≥90% drug pick-up adherence at baseline. Compared with baseline, the proportion with MPR ≥90% increased numerically at both weeks 24 and 48 (85% and 80%, respectively); statistical significance was achieved at 24 weeks ($P = 0.022$) but not 48 weeks ($P = 0.092$). MPR was not significantly correlated with viral suppression at 24 weeks (r = 0.306, $P = 0.054$) but significantly correlated at 48 weeks (r = 0.357, $P = 0.024$).

Hair samples were provided by 23% of participants. Because of this low uptake, antiretroviral drug concentrations were not measured. Retention in care was 98% at 24 weeks and 88% at 48 weeks.

TABLE 1. Demographic Characteristics of iCARE Nigeria Study Participants (N = 40)

	Total, n (%)
Age	
Mean (SD)	19.9 (2.5)
Median (range)	19 (15–24)
Sex	
Male participants	20 (50.0)
Female participants	20 (50.0)
Ethnic group	
Hausa	1 (2.5)
Igbo	4 (10.0)
Yoruba	35 (87.5)
Religion	
Christian	27 (67.5)
Islam	13 (32.5)
Highest level of education	
No formal education	1 (2.5)
Primary school	1 (2.5)
Junior secondary school	0 (0)
Senior secondary school	24 (60.0)
Tertiary institution	14 (35.0)
Mode of infection	
Behavioral	11 (27.5)
Perinatal	22 (55.0)
Blood transfusion/other medical	2 (5.0)
Unknown	5 (12.5)
Viral load <200 copies/mL	
Yes (suppressed)	14 (35.0)
No (viremic)	26 (65.0)
Visual analog scale	
≥90% adherent	17 (42.5)
Medication possession ratio	
≥90% adherent	25 (62.5)
Antiretroviral regimen	
First line	26 (65.0)
Second line	14 (35.0)
Cell phone (baseline)	
Own/possess cell phone	26 (65.0)
Did not own/possess cell phone	14 (35.0)

First-line regimens = 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus efavirenz (17), dolutegravir (8), or nevirapine (1). Second-line regimens = 2 NRTIs plus atazanavir/ritonavir (11) or lopinavir/ritonavir (3).

TABLE 2. Participants With Viral Suppression Overall and in Subgroups (N = 40)

Virological Suppression (Copies/mL)	Baseline, n (%)	24 Weeks, n (%)	48 Weeks, n (%)
Overall			
<200	14 (35)	27 (68)†	24 (60)*
<1000	19 (48)	31 (78)†	28 (70)*
Perinatally infected (<200)	5 (23)	15 (68)	15 (68)
Nonperinatally infected‡ (<200)	5 (45)	7 (64)	6 (55)
First-line regimen (<200)	11 (42)	21 (81)	18 (69)
Second-line regimen (<200)	3 (21)	6 (43)	6 (43)
Owned cell phone (<200)	10 (38)	16 (62)	16 (62)
Did not own cell phone (<200)	4 (29)	11 (79)	8 (57)

P values represent exact McNemar tests for viral suppression indicating differences from baseline. Participants who did not complete a visit at 48 weeks were considered nonvirologically suppressed. Statistical tests were not performed for subgroups given small cell counts.

*$P < 0.05$.

†$P < 0.01$.

‡Excluding 7 participants who reported blood transfusion (2) or unknown (5) mode of transmission.

Feasibility, Acceptability, and Satisfaction

We identified 9 peer navigators (8 original and one replacement) with a mean age of 22.6 years (3.7). The assignment ratio of peer navigators to peers was 1:5. Each peer navigator contacted their assigned peers an average of 1.8 times in each 2-week period, which was above the expected average of at least one contact. The proportion of participants who were provided a phone at some point during the study was 40%. After an adjustment period because of technical challenges, text message reminders were successfully deployed to 100% of participants on a consistent basis by study week 7.

Regarding acceptability, at week 48, 5% of participants reported the text messages as sometimes or always "intrusive or bothersome," and 10% found peer navigation sometimes or always "intrusive or bothersome." No participant experienced inadvertent disclosure of HIV status or any other unexpected adverse events because of either aspect of the intervention. At 48 weeks, 100% (n = 37 of the 37 retained) of participants indicated that they were very satisfied or mostly satisfied with the combination intervention and 100% (n = 37 of 37) of participants would refer a friend to receive it.

DISCUSSION

In a heterogeneous cohort of YWH in Nigeria, the iCARE combination intervention, comprising daily 2-way text message reminders and peer navigation, led to a 6-fold increase in the odds of viral suppression from baseline to 48 weeks. The combination intervention was feasible and acceptable with high satisfaction and retention in HIV care documented. These remarkable results were obtained although the last 14 weeks of the study occurred during the coronavirus disease 2019 (COVID-19) pandemic. Two of the participants with viral nonsuppression at week 48 had achieved viral suppression at week 24, which they subsequently lost because of interstate travel lockdown that affected antiretroviral drug pick-up from the clinic pharmacy. Given the increasing popularity of text messaging across sub-Saharan Africa,[38] the iCARE combination intervention may have broad relevance and impact if our pilot results are confirmed in larger studies.

Previous studies in 15- to 24-year-old patients across sub-Saharan Africa highlight the challenges of influencing HIV care outcomes in this population. In a retrospective cohort study in South Africa, loss to follow-up did not significantly improve among youth, aged 16–24 years, who received a community health worker–led, nurse-assisted intervention.[25] Another study, conducted in Uganda, showed no significant effect of one-way or 2-way text messaging on ART adherence among YWH aged 15–22 years.[25] Our study differs from these earlier studies in that we deployed 2 distinct interventions (2-way text message reminders and peer navigation) concurrently and used viral suppression as the primary outcome measure. We chose a combination approach on the premise that automated text message reminders would address some drivers of poor ART adherence, such as forgetfulness, whereas barriers related to stigma, mental health, or social instability would be better addressed by needs-based peer support. This combination approach may explain our positive results in a heterogeneous youth population of perinatally infected and nonperinatally infected youth, young male and young female participants, those on first- and second-line regimens, and those with or without personal phones. In addition, it is likely that the selected text-messaging approach independently promoted success because it was based on a validated, CDC-recommended intervention (TXTXT),[14] which we further adapted to the study population.[28] Nevertheless, the fact that 40 percent of YWH in our study was viremic, dead, or lost to follow-up, despite 48 weeks of the combination intervention, suggests that additional interventions are needed for some YWH. Baseline antiretroviral drug resistance may explain the poor outcomes in some of these youth,[39] along with intractable barriers to ART access and adherence that we documented such as food insecurity, housing instability, and nondisclosure.

By integrating formative research, we designed an intervention that prioritized the needs and preferences of YWH, while factoring in local social and health infrastructure realities. Thus, we assigned 5 YWH to each peer navigator. This standardization is important, given heterogeneity around the operationalization of peer support in the literature.[21] The peer navigators were volunteers and received nominal stipends, which makes the intervention scalable and sustainable. In addition, as recommended by YWH in the formative focus groups, we selected navigators who were older, on average, than participants (mean age of 22.6 versus 19.9 years). This aligns with local culture, which assigns greater responsibility to older individuals, and is similar to the Zvandiri model in Zimbabwe, where 18- to 24-year-old individuals served as treatment supporters to 10- to 15-year-old adolescents.[40] Each youth in our study was asked to choose the text message they received, thereby supporting

youths' desire for autonomy.[17] Finally, the study intervention did not require clinic visits. As a result, it was convenient for youth who lived far from the study site to take part.

The age range of participants in our study spans the latter half of adolescence into young adulthood. As such, an important question is whether the results can be extrapolated to adolescents younger than 15 years. We caution against such extrapolation in the absence of evidence. Compared with 15- to 24-year-old participants, adolescents younger than 15 years are at a different cognitive developmental stage and have different challenges and needs with treatment adherence when confronted with a chronic condition such as HIV.[41–43] Moreover, it is doubtful that the younger adolescents can be expected to have, or maintain, personal phones for the combination intervention. There are already interventions targeting adolescents younger than 15 years, such as facility-based peer support[44] and community-based peer support,[45] without text messaging.

Our study is not without limitations. First, we enrolled only 40 YWH in this single-arm study; however, this sample size and design were adequate to determine whether the combination intervention is sufficiently promising to justify advancing it to the second phase of the iCARE study, a larger, randomized trial of the intervention's effectiveness. Second, although there were improvements in self-reported adherence by VAS, the correlations with viral suppression were weak and not statistically significant; however, the levels of correlation are consistent with previous research among PWH.[30] Drug pick-up adherence (MPR) correlated with virologic suppression at week 48, although the numerical improvement in adherence at this time point did not achieve statistical significance. Reasons for these results may include the small sample size and inherent limitations of adherence measures, such as VAS and MPR, which do not capture actual drug ingestion.[30,46,47] We had planned to directly measure antiretroviral drug levels in hair,[48] but less than a quarter of participants provided hair sample, likely linked to Nigerian men's preference for short hair plus fears among Nigerians that hair may be used for rituals.[49] Antiretroviral drug levels in dried blood spots will be used to objectively measure adherence in the next phase of our study. Finally, it remains to be seen whether already stretched health systems will be able to provide resources such as mobile phones that the study purchased for 40 percent of participants. Overall, the combination intervention consumed little resources, and importantly, remarkable results were obtained at IDI/CoMUI, which has a well-established youth club. Youth-friendly services are advocated for ART programs that cater to YWH because such services may improve outcomes.[50,51] Our results suggest that the combination intervention used in this study may be synergistic with other youth-targeted programs and, thereby, save more lives and costs in the long run. Cost-effectiveness studies are needed to clarify this.

In conclusion, this 48-week pilot study demonstrated that the iCARE combination intervention is promising for improving ART outcomes among YWH aged 15–24 years in Nigeria. Based on these positive results, a large, fully powered, randomized, step-wedge study, with implementation science and cost-effectiveness components, is underway at 6 sites in 4 Nigerian cities.

ACKNOWLEDGMENTS

The authors acknowledge all iCARE Nigeria research staff, including Hadeis Safi and Sergio Tundo (Ann and Robert H. Lurie Children's Hospital), Dr. Tobi Olaniyi, Mr. Muyiwa Ojo-Osagie, and Mr. Chuks (Omoruyi University of Ibadan). The authors also thank Prof. Sulaimon Akanmu (Lagos University Teaching Hospital), Dr. Sylvia Adebajo (Population Council), Mr. Jude Onumabor, and the Nigerian health authorities. This study could not have been conducted without the selfless contributions of study volunteers and the general YWH population at IDI/CoMUI.

REFERENCES

1. Federal Ministry of Health Nigeria. *National Guidelines for HIV Prevention, Treatment and Care*; 2016. Available at: https://www.prepwatch.org/wp-content/uploads/2017/08/nigeria_national_guidelines_2016.pdf. Accessed September 5, 2020.
2. INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med.* 2015;373:795–807.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365:493–505.
4. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med.* 2015;373:808–822.
5. *UNAIDS Fast Track-Ending the AIDS Epidemic by 2030*. Available at: https://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf. Accessed September 5, 2020.
6. DeSilva MB, Merry SP, Fischer PR, et al. Youth, unemployment, and male gender predict mortality in AIDS patients started on HAART in Nigeria. *AIDS Care.* 2009;21:70–77.
7. Mark D, Armstrong A, Andrade C, et al. HIV treatment and care services for adolescents: a situational analysis of 218 facilities in 23 sub-Saharan African countries. *J Int AIDS Soc.* 2017;20(Suppl 3):21591.
8. Auld AF, Agolory SG, Shiraishi RW, et al. Antiretroviral therapy enrollment characteristics and outcomes among HIV-infected adolescents and young adults compared with older adults–seven African countries, 2004-2013. *MMWR Morb Mortal Wkly Rep.* 2014;63:1097–1103.
9. *UNAIDS : On the Right Track towards the Global Target*. Available at: https://reliefweb.int/sites/reliefweb.int/files/resources/90_90_90_Progress_ReportFINAL.pdf. Accessed September 5, 2020.
10. Lester R, Karanja S. Mobile phones: exceptional tools for HIV/AIDS, health, and crisis management. *Lancet Infect Dis.* 2008;8:738–739.
11. Adetunji AA, Muyibi SA, Imhansoloeva M, et al. Mobile phone use for a social strategy to improve antiretroviral refill experience at a low-resource HIV clinic: patient responses from Nigeria. *AIDS Care.* 2017;29:575–578.
12. Nigerian Communications Commission. *Subscriber Statistics*. Available at: https://www.ncc.gov.ng/statistics-reports/subscriber-data. Accessed August 21, 2020.
13. Centers for Disease Control. *Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention*.Available at: https://urldefense.com/v3/__https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-text-messaging-txtxt-good-ma.pdf__;!!Dq0X2DkFhyF93HkjWTBQKhk!FhItjkQS0WFip37wWV8Tstd3201X-OvHhbMsstpakeb9PRwejGDeNsLhUGGfY2s7tNBfBA$. Accessed September 13, 2020.
14. Garofalo R, Kuhns LM, Hotton A, et al. A randomized controlled trial of personalized text message reminders to promote medication adherence among HIV-positive adolescents and young adults. *AIDS Behav.* 2016;20:1049–1059.
15. Resnick MD, Catalano RF, Sawyer SM, et al. Seizing the opportunities of adolescent health. *Lancet.* 2012;379:1564–1567.
16. Steinberg L, Monahan KC. Age differences in resistance to peer influence. *Dev Psychol.* 2007;43:1531–1543.
17. Adejumo OA, Malee KM, Ryscavage P, et al. Contemporary issues on the epidemiology and antiretroviral adherence of HIV-infected adoles-

cents in sub-Saharan Africa: a narrative review. *J Int AIDS Soc.* 2015;18: 20049.
18. Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. *Lancet.* 2016;387: 2423–2478.
19. World Health Organization. *HIV and Adolescents: Guidance for HIV Testing and Counselling and Care for Adolescents Living with HIV*. Geneva, Switzerland: World Health Organization; 2013. Available at: https://www.who.int/hiv/pub/guidelines/adolescents/en/. Accessed September 13, 2020.
20. Ammon N, Mason S, Corkery JM. Factors impacting antiretroviral therapy adherence among human immunodeficiency virus-positive adolescents in sub-Saharan Africa: a systematic review. *Public Health*. 2018;157:20–31.
21. Mark D, Hrapcak S, Ameyan W, et al. Peer support for adolescents and young people living with HIV in sub-saharan africa: emerging insights and a methodological agenda. *Curr HIV/AIDS Rep.* 2019;16:467–474.
22. *UN Joint Programme on HIV/AIDS (UNAIDS). UNAIDS Estimates*. 2018. Available at: https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf. Accessed July 4, 2020.
23. Casale M, Carlqvist A, Cluver L. Recent interventions to improve retention in HIV care and adherence to antiretroviral treatment among adolescents and youth: a systematic review. *AIDS Patient Care STDS*. 2019;33:237–252.
24. Ojwang VO, Penner J, Blat C, et al. Loss to follow-up among youth accessing outpatient HIV care and treatment services in Kisumu, Kenya. *AIDS Care.* 2016;28:500–507.
25. Grimsrud A, Lesosky M, Kalombo C, et al. Implementation and operational research: community-based adherence clubs for the management of stable Antiretroviral therapy patients in cape town, South Africa: a cohort study. *J Acquir Immune Defic Syndr.* 2016;71:e16–e23.
26. Mills EJ, Lester R, Thorlund K, et al. Interventions to promote adherence to antiretroviral therapy in Africa: a network meta-analysis. *Lancet HIV*. 2014;1:e104–e111.
27. Chaiyachati KH, Ogbuoji O, Price M, et al. Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. *AIDS*. 2014;28(Suppl 2):S187–S204.
28. Johnson AK, Kuti K, Kuhns L, et al. *Adaption of Evidence Based Approaches to Promote HIV Testing and Treatment Engagement Among High Risk Nigerian Youth*. Abstract W09, Session 75. Presented at AIDS Impact 2019, London, United Kingdom.
29. *Nigeria Federal Ministry of Health Guidelines for Young Persons' Participation in Research and Access to Sexual and Reproductive Health Services in Nigeria*. Available at: https://www.popcouncil.org/uploads/pdfs/2014HIV_YoungPersonsSRH-Nigeria.pdf. Accessed October 18, 2020.
30. Finitsis DJ, Pellowski JA, Huedo-Medina TB, et al. Visual analogue scale (VAS) measurement of antiretroviral adherence in people living with HIV (PLWH): a meta-analysis. *J Behav Med.* 2016;39:1043–1055.
31. Fairman K, Motheral B. Evaluating medication adherence: which measure is right for your program?. *J Manag Care Pharm.* 2000;6: 499–504.
32. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. *J Clin Epidemiol.* 2004;57:1107–1110.
33. McMahon JH, Jordan MR, Kelley K. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. *Clin Infect Dis.* 2011;52:493–506.
34. Gandhi M, Bacchetti P, Ofokotun I, et al. Antiretroviral concentrations in hair strongly predict virologic response in a large human immunodeficiency virus treatment-naive clinical trial. *Clin Infect Dis.* 68:1044–1047.
35. Vollmer WM, Xu M, Feldstein A, et al. Comparison of pharmacy-based measures of medication adherence. *BMC Health Serv Res.* 2012;12:155.
36. Kahana SY, Rohan J, Allison S, et al. A meta-analysis of adherence to antiretroviral therapy and virologic responses in HIV-infected children, adolescents, and young adults. *AIDS Behav.* 2013;17:41–60.
37. Attkisson CC, Greenfield TK. Client satisfaction questionnaire-8 and service satisfaction scale-30. In: Maruish ME, ed. *The Use of Psychological Testing for Treatment Planning and Outcome Assessment*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc; 1994:402–420.
38. Pew Research Center. *Cell Phones in Africa: Communication Lifeline [Internet]*. Washington, DC: Pew Research Center; 2015. Available at: http://www.pewglobal.org/2015/04/15/cell-phones-in-africa-communication-lifeline. Accessed September 21, 2020.
39. Boender TS, Hoenderboom BM, Sigaloff KC, et al. Pretreatment HIV drug resistance increases regimen switches in sub-Saharan Africa. *Clin Infect Dis.* 2015;61:1749–2175.
40. Willis N, Milanzi A, Mawodzeke M, et al. Effectiveness of community adolescent treatment supporters (CATS) interventions in improving linkage and retention to care, adherence to ART and psychosocial well-being: a randomized trial among adolescents living with HIV in Zimbabwe. *BMC Public Health.* 2019;19:117.
41. Koech E, Teasdale CA, Wang C, et al. Characteristics and outcomes of HIV-infected youth and young adolescents enrolled in HIV care in Kenya. *AIDS.* 2014;28:2729–2738.
42. Bygrave H, Mtangirwa J, Ncube K, et al. Antiretroviral therapy outcomes among adolescents and youth in rural Zimbabwe. *PLoS One.* 2012;7:e52856.
43. Lamb MR, Fayorsey R, Nuwagaba-Biribonwoha H, et al. High attrition before and after ART initiation among youth (15-24 years of age) enrolled in HIV care. *AIDS.* 2014;28:559–568.
44. Mark D, Bloch K, Cluver L, et al. The power of peers: multi-country analysis of adolescent viral suppression in sub-Saharan Africa. Abstract WEPEE721. Presented at: The International AIDS Conference; 2018; Amsterdam.
45. PEPFAR Solutions Database. *Operation Triple Zero: Empowering Adolescents and Young People Living with HIV to Take Control of Their Health in Kenya*; 2018. Available at: https://www.pepfarsolutions.org/solutions/2018/10/30/operation-triple-zero-empowering-adolescents-and-young-people-living-with-hiv-to-take-control-of-their-own-health. Accessed September 5, 2020.
46. Ahonkhai AA, Banigbe B, Adeola J, et al. High medication possession ratios associated with greater risk of virologic failure among youth compared with adults in a Nigerian cohort. *J Acquir Immune Defic Syndr.* 2018;78:322–328.
47. Meloni ST, Agaba P, Chang CA, et al. Longitudinal evaluation of adherence, retention, and transition patterns of adolescents living with HIV in Nigeria. *PLoS One.* 2020;15:e0236801.
48. Tabb ZJ, Mmbaga BT, Gandhi M, et al. Antiretroviral drug concentrations in hair are associated with virologic outcomes among young people living with HIV in Tanzania. *AIDS.* 2018;32:1115–1123.
49. Nwogu JN, Babalola CP, Ngene SO, et al. Willingness to donate hair samples for research among people living with HIV/AIDS attending a tertiary health facility in Ibadan, Nigeria. *AIDS Res Hum Retroviruses.* 2019;35:642–648.
50. Grieb SM, Kerrigan D, Tepper V, et al. The clinic environment as a form of social support for adolescents and young adults living with HIV. *AIDS Patient Care STDs.* 2018;32:208–213.
51. MacKenzie R, van Lettow M, Gondwe C, et al. Greater retention in care among adolescents on antiretroviral treatment accessing "Teen Club" an adolescent-centred differentiated care model compared with standard of care: a nested case control study at a tertiary referral hospital in Malawi. *J Int AIDS Soc.* 2017;20:e25028.