Changes in adherence and viral load suppression among people with HIV in Manila: Outcomes of the Philippines Connect for Life Study

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Abstract

The Philippines HIV epidemic is among the fastest growing globally. Infections among men who have sex with men (MSM) are rising at an alarming rate, necessitating targeted evidence-based interventions to retain people living with HIV (PLHIV) in care, support adherence, and reach viral suppression. We conducted a 48-week prospective cohort study of 462 participants in which we provided a mobile health (mHealth) adherence support intervention using the Connect for Life platform. We observed an improvement in adherence, with the proportion of participants taking more than 95% of their antiretroviral therapy (ART) doses increasing from 78.6% at baseline to 90.3% at 48 weeks. Among treatment experienced participants, adherence improved significantly (McNemar's test=21.88, P<0.001). Viral load suppression did not change, with 92.6% suppression at baseline and

92.0% at 48 weeks. Illicit drug use was associated with reduced adherence (aOR=0.56, 95%CI 0.31-1.00, P=0.05) and being on second-line therapy was associated with poor viral load suppression (aOR=0.33, 95%CI 0.14-0.78, P=0.01). Quality of life (QOL) improved following ART initiation, from a mean of 84.6 points (of a possible 120) at baseline to 91.01 at 48 weeks.

Due to technical issues, fidelity to the intended intervention was low, with 22.1% (102/462) of participants receiving any voice calls and most others receiving a scaled-back SMS intervention. The mHealth intervention did not have any observed effect on adherence or on viral load suppression. While evidence of effectiveness of mHealth adherence interventions is mixed, these platforms should continue to be explored as part of differentiated treatment support services.

Keywords: mHealth. Adherence. HIV. Antiretroviral Therapy. Philippines.

Background

The HIV epidemic in the Philippines is one of the fastest growing HIV epidemics globally, with a doubling of the number of new HIV infections and the number of AIDS deaths increasing nearly by 400% from 2010 to 2020.[1,2] Most new and existing HIV infections in the Philippines occur among men who have sex with men (MSM).[2]

To slow the spread of HIV, the Philippines must continue to progress toward the Joint United Nations Program on HIV/AIDS (UNAIDS) 95-95-95 goals within all subpopulations and age groups. Currently, in the Philippines 64% of people living with HIV (PLHIV) know their status, 41% of those who are HIV positive are on antiretroviral therapy (ART), and the proportion of PLHIV with suppressed viral loads is unknown.[3–5] HIV care and treatment is freely available through the government-funded Philippine Health Insurance Corporation (PhilHealth) Outpatient HIV/AIDS Treatment (OHAT) package.[6]

mHealth for Medication Adherence Support: To achieve viral suppression, patients on ART must take their treatment consistently. However, in clinical practice achieving and maintaining optimal ART adherence is challenging.[7,8] Early clinical studies reported that ≥95% adherence to ART was required to achieve and maintain viral suppression [9,10]. More recent studies have shown that virologic suppression may be achieved with adherence levels <95%, however this is dependent on the duration of treatment and the ART regimen [11–13]. ART non-adherence has been linked to the development of ART resistance,[14,15] progression to AIDS,[16] and death.[17]

Several key factors influencing ART adherence are well documented in the literature, including medication side effects, substance abuse, presence of social support, and time on treatment.[7,8,18–21] In the Philippine context, issues of stigma and discrimination have also been documented as a major barrier to medication adherence. [22–25]

As mobile phone technologies for health (mHealth) have become increasingly popular in the global health and development sectors, clinical trials have shown that mHealth approaches have promise in improving self-management of chronic disease including adherence to HIV medications [26–30]. A 2017 systematic review and meta-analysis assessing interventions to improve adherence to ART found that SMS interventions were superior to standard of care (OR 1.48, CrI 1.00-2.16), and that multiple interventions had additive affects.[31] Systematic reviews show mixed outcomes of mHealth interventions and highlight the need for more rigorous evaluation methods and longer follow-up periods.[32–38]

The WHO Consolidated Guidelines on ART recommend using mHealth approaches to support HIV care and treatment and improve adherence. The 2016 guidelines endorsed mobile phone text messages as low-cost interventions that have demonstrated benefit in improving adherence and viral suppression and are backed by “moderate evidence.”[39]

During this study, we provided participants with an mHealth adherence support intervention using a platform called Connect for Life. The platform is able to send automated messages to participants via their mobile phones through interactive voice response system (IVRS) call flows or through SMS text messages.[40] Participants received varying levels of exposure to the intervention, with the frequency of contact and types of messaging received being dependent on a combination of personal preference and contextual factors.

Prior to roll out in the Philippines, the Connect for Life platform was piloted for use in maternal health and HIV programs in India and Uganda.[41–44] To adapt the intervention for the local setting and target population In the Philippines, we applied a mixed methods approach guided by the Behavior Change Wheel (BCW) framework and the information, motivation, and behavioral skills (IMB) model of adherence.[45–47] The BCW is a method for characterizing and developing behavior change interventions based on a comprehensive causal analysis of the behavior, while the IMB model includes three primary constructs that influence behavior changes: information and knowledge about the behavior; the individual's motivation to perform the behavior; and the behavioral skills necessary to perform the behavior.

In the context of the emerging HIV crisis among MSM in the Philippines, there is an imperative to expand options for tailored HIV prevention and treatment support. While other studies have found high levels of feasibility and acceptability of SMS interventions targeted toward HIV-positive MSM in the United States, in Peru, and in Asia,[48–51] there is a lack of data on interventions to improve adherence and treatment outcomes among HIV-positive MSM. Furthermore, few mHealth interventions for MSM have been evaluated in Asia and none in the Philippines. In this paper we present the outcomes of a prospective cohort study of HIV patients in the Philippines, describing

adherence to medication, retention in care, and viral load suppression. We examine various factors affecting these outcomes including the mHealth adherence support intervention received.

Methods

We conducted a prospective cohort study, collecting data at four time points: baseline, 12-, 24-, and 48 weeks. The study was conducted at the Sustained Health Initiatives of the Philippines (SHIP) clinic, a low-cost, private facility providing HIV care and treatment to people in Metro Manila, Philippines. Approximately 98% of SHIP's clients are MSM, with an average age of 30 years at initial consultation.

Recruitment into the Connect for Life study occurred in-person at the SHIP clinic from October 2016 to December 2017. Eligible participants were HIV-positive, receiving ART at the study site, could speak and read English, and had a mobile phone. The study coordinator approached patients attending their routine visits while they were in the clinic waiting room. Patients were not approached or screened on days the study coordinator was not available, or if they bypassed the waiting room.

During the study, participants received a personalized combination of services, including automated pill reminders, appointment reminders, health tips, and adherence feedback messages delivered by voice call or SMS on the patient's preferred time and day. Based on findings from formative stages of the project, we planned to provide daily pill reminder calls to participants who were on ART for less than 6 months and weekly reminder calls to those on ART for 6 months or longer.[45]

Ethical clearance for the study was obtained from the University of the Philippines Manila Research Ethics Board (protocol number 2016-265-01) and from the London School of Hygiene and Tropical Medicine (reference number 11631). All participants provided written consent prior to inclusion in the study.

Objectives: The primary objective of this observational, single-arm study was to describe the adherence to medication, viral load suppression, and retention in care of the patient population participating in the Connect for Life mobile phone adherence support demonstration project. The secondary objectives were: to describe the Quality of Life and the HIV-related Knowledge, Attitudes, and Practices of participants; to describe the clinical outcomes of participants including treatment failure (switch to second-line), and AIDS-related mortality; and to identify factors that affected patient adherence and treatment outcomes.

Data sources/measurements: Laboratory results, diagnoses, dispensing, and other clinical information were extracted from patient charts by the study coordinator. Each participant completed three questionnaires at each visit: HIV-related knowledge, attitudes and practices (KAP) adapted from the Brief HIV Knowledge Questionnaire (HIV-KQ-18)[52]; the WHO HIV Quality of Life questionnaire (WHOQOL-HIV BREF)[53,54]; and an adherence questionnaire that was adapted from the AIDS Clinical Trials Group adherence instrument.[21] All questionnaires were in English. The questionnaires were self-administered, with assistance from the study coordinator as requested. Where questionnaires had blank or missing or incomplete fields, all available data points were included in the analysis.

Outcomes: The main outcomes of interest were adherence, viral load suppression, and retention in care. Secondary outcomes included quality of life and HIV-related knowledge. Outcomes were measured over time with all observations from the 12-, 24-, and 48-week visits considered as outcomes.

Key variables were defined as follows:

- Adherence: At each study visit, using a visual analogue scale (VAS) participants reported the proportion of ART doses taken in the prior 30 days as 0–100%. This continuous variable was converted into a binary variable with those reporting 95% or greater categorized as adherent.
- Viral Load suppression: A binary variable defining suppression as HIV viral load lower than detectable limit of lab assay (<50 copies/ml). All viral load tests were conducted as routine standard of care (not provided by the study) and all available test results were extracted from patient files. Only viral load tests that were collected at least 3 months after treatment initiation were included.
- Retention in care: Proportion of participants alive and in care ("not in care" defined as not having returned for more than 30 days after last scheduled clinic visit or refill).
- Treatment experience at enrollment: A binary variable defining treatment experience as having initiated ART more than 6 months prior to study enrollment date.
- Exposure to the intervention: A continuous variable defined as the total number of days the patient received one or more SMS text messages or calls from the Connect for Life platform during the study. This was then converted into a categorial variable representing level of exposure with High (96+ days of contact), Medium (48-95 days of contact), Low (12-47 days of contact), and no exposure (<12 days). These cut points serve as rough proxies for monthly, weekly, or daily contact, with the three categories of exposure (excluding no exposure) each representing at least 50 individuals.
- QOL: A continuous variable of up to a maximum of 120 points, scored as per WHOQOL-HIVBREF questionnaire.[53,54]
- KAP: Knowledge was categorized as a continuous variable, based on a 16-item dichotomous response (true/false) questionnaire. The questionnaire had two additional sections about sexual activities, alcohol and drug use which included dichotomous, categorical, and continuous variables.

Statistical analysis: Demographic and clinical characteristics were described as a mean or proportion with a 95% confidence interval. Descriptive analyses of adherence and viral load outcomes were performed for the entire cohort, and then according to: (1) intervention exposure category, (2) adherence above or below 95% at baseline, and (3) treatment experience of more or less than 6 months at enrollment. We hypothesized that higher level of exposure to the intervention could lead to greater improvements in the key outcomes. We also hypothesized that treatment naïve participants and those with poor adherence at baseline may benefit more than others from receiving reminders to achieve adequate adherence and viral load suppression.

Adjusted odds ratios were estimated using a generalized estimating equations (GEE) model with an exchangeable correlation structure and robust variance. GEE was selected to allow for clustering of outcomes within an individual. The model included intervention exposure, treatment experience, baseline adherence, and other factors which had a p-value <0.1 in unadjusted univariate analyses (with some factors excluded a priori due to collinearity). For both main outcomes, all observations from follow-up visits were included in outcome analyses, and the models adjusted for baseline adherence and baseline viral load, respectively. Wald tests were used to calculate p-values of each variable.

Several sensitivity analyses were conducted. Both univariable and multivariable analyses were reproduced using continuous variables for intervention exposure (unique number of days participant received call or SMS) and adherence (percent adherence from 0 to 100) in place of the respective categorical and binary variables. The analyses were also reproduced using mixed-effects logistic regression models instead of GEE. Finally, the descriptive and inferential analyses were reproduced using an intention to treat approach, in which the dataset was updated to include data points for participants who were lost to follow-up or who died with the assumption that they were non-adherent

and virally unsuppressed for the period from the time they became lost to follow-up tor deceased until the date when they would have completed the study.

Results

Participants

Approximately 675 participants were receiving HIV care at the study site during the recruitment period. 485 patients were approached by the study coordinator. Of those approached 95.7% (464/485) agreed to be screened for enrollment, and 95.3% (462/485) met the eligibility criteria and consented to participate (**Figure 1**).

Reasons for refusal (21/485, 4.3%) included no need or desire for adherence support, not wanting to receive messages or calls on their mobile phone, privacy concerns, and inconsistent access to mobile phone due to frequent international travel. Of the 0.4% (2/464) of the patients who were excluded based on screening, one was ineligible because he did not speak English and the other did not have a mobile phone. Of the participants enrolled, 0.1% (3/462) withdrew, 0.1% (3/462) died, 3.7% (17/462) transferred to another clinic for their care, 3.9% (18/462) were lost to follow-up (missed two consecutive visits), and the remaining 91.1% (421/462) completed the study.

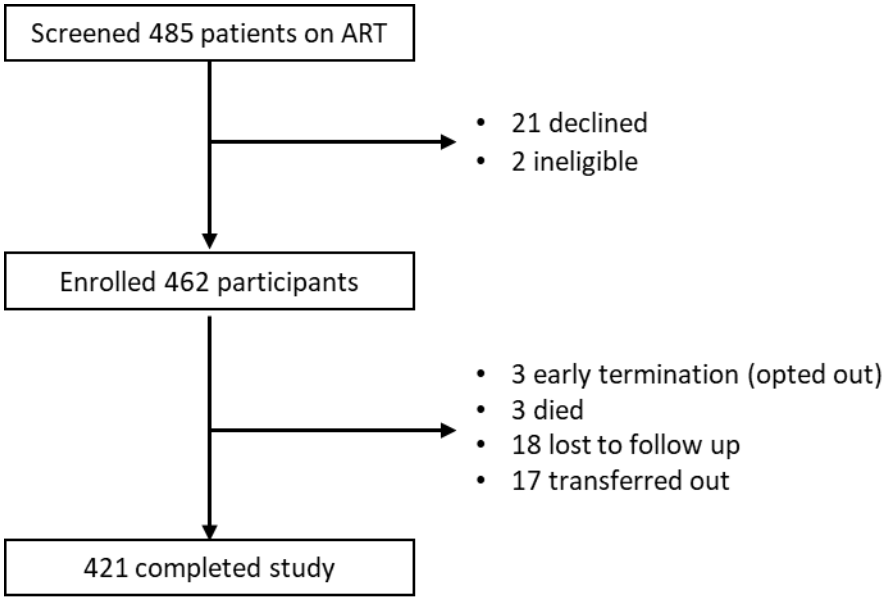

Figure 1. Recruitment and study completion of patient cohort

Demographic factors, clinical characteristics and behavioral practices of the study participants are described in **Table 1.** As the study site caters to young MSM, all but one of the participants in the study (461/462, 99.8%) were male and only 1.5% of participants (7/462) were heterosexual. Most participants were treatment experienced, with the mean time on ART among experienced participants being 2.77 years (SD 2.0). The mean age at enrollment was 32.4 years (SD 5.7). Most participants were university graduates (397/462, 85.9%) and most were either employed or students (422/462, 91.3%).

Notably, nearly half of all participants (227/462, 49.1%) had not disclosed their HIV status to a family member or friend. Furthermore, a substantial proportion of participants (94/462, 20.4%) worked in the Business Process Outsourcing (BPO) sector, a key economic sector in which third-party vendors provide services remotely (e.g. contact centers, back-office services, data transcription, and information technology), usually to multinational corporations. Due to the variable nature of work schedules for BPO workers and lack of privacy due to working conditions in call center settings, this group faces unique barriers to adherence.

Table 1. Baseline Characteristics of Study Participants (N=462).

Characteristics		Number	(%)
Gender	Male	461	99.78
	Female	1	0.22
Age	18-24	23	4.98
Mean: 32.4 years (SD 5.7)	25-29	132	28.57
	30-39	262	56.71
	40+	45	9.74
Education	Elementary or less	11	2.38
	High School/Vocational	21	4.55
	College/University	345	74.68
	Post-Graduate	52	11.26
	Unknown/Did not report	33	7.14
Employment	Employed	422	91.34
	Unemployed	40	8.66
Sexual Orientation	Bisexual	139	30.09
	Heterosexual	9	1.95
	Homosexual	313	67.75
	Pansexual	1	0.22
Civil Status	Married/Common-law partner	21	4.55
	Single	439	95.02
	Unknown/Did not report	2	0.43
Serodiscordant Relationship	Not in a relationship	290	62.77
	Seroconcordant relationship (both HIV+)	50	12.24
	Serodiscordant relationship (partner is HIV-)	75	16.23
	Unknown/Did not report	47	10.17
Disclosure of HIV Status to family/friend	Disclosed	146	31.60
	Not disclosed	227	49.13
	Unknown/Did not report	89	19.26
Time on ART, years	<30 days	45	9.74
	1-6 months	30	6.49
	6 months – 1 year	39	8.44
	1-2 years	86	18.61
	2-4 years	163	35.28
	>4 years	99	21.43
Nadir CD4 (cells/mm3)	0-199	177	38.31
	200-499	253	54.76
	500+	32	6.93
ART Regimen	First Line	393	85.06
	Second/Third Line	69	14.94
Condom Usage in last 6 months	Always	184	39.83
	Sometimes/Most of the time	169	36.58
	Never	88	19.05
	N/A (not sexually active)	21	4.55
Transactional Sex	Never had transactional sex	434	93.94
	Ever had transactional sex	26	5.63
	Unknown/Refused	2	0.43
Sexual Partners in last 6 months	None	97	26.01
	One	147	39.41
	2-9	106	28.42
	10 or more	23	6.17
Problem alcohol use*	No	388	85.84
	Yes	64	14.16
Injection Drug Use (ever)	No	406	87.88
	Yes	56	12.12
Any Drug Use (3 months preceding enrollment)	No	386	83.55
	Yes	76	16.45
Baseline Viral Load **	Detectable (>=50 copies/ml)	21	4.55
	Undetectable (<50 copies/ml)	262	56.71
	No VL data at baseline	179	38.74

**Problem alcohol use defined as two or more episodes of heavy episodic or 'binge' drinking (>five drinks) in the prior month or >14 drinks per week on average.*[55,56]
*** Conducted at the baseline visit or in six months prior to enrollment.*

Delivery of the Adherence Support Intervention

The intended intervention would provide daily pill reminder calls to participants who were on ART for less than 6 months and weekly reminder calls to those on ART for 6 months or longer.[45] Due to technical issues, fidelity to the intended intervention was low, with only 22.1% (102/462) of participants receiving any voice calls and most others receiving a scaled-back SMS intervention (**Figure 2**). Technical issues were first identified in the second month of the study, at which point new enrollment was paused for approximately three months while the study team assessed the cause of the issue. Ultimately, the issue was characterized as a dual tone multi-frequency (DTMF) malfunction – i.e., a problem with the tones not being transmitted or recognized when pressing digits on the handset to navigate interactive touch-tone menu. This was attributed to issues in the telecommunications system that neither the telecommunications provider nor the Connect for Life developers could resolve. When enrollment was resumed, participants were offered SMS text messages rather than IVRS voice call services. Because not all participants experienced technical challenges with voice calls, those who had a strong preference for voice calls could opt in, and they were counselled about the possibility of technical challenges and how to report issues to the study team.

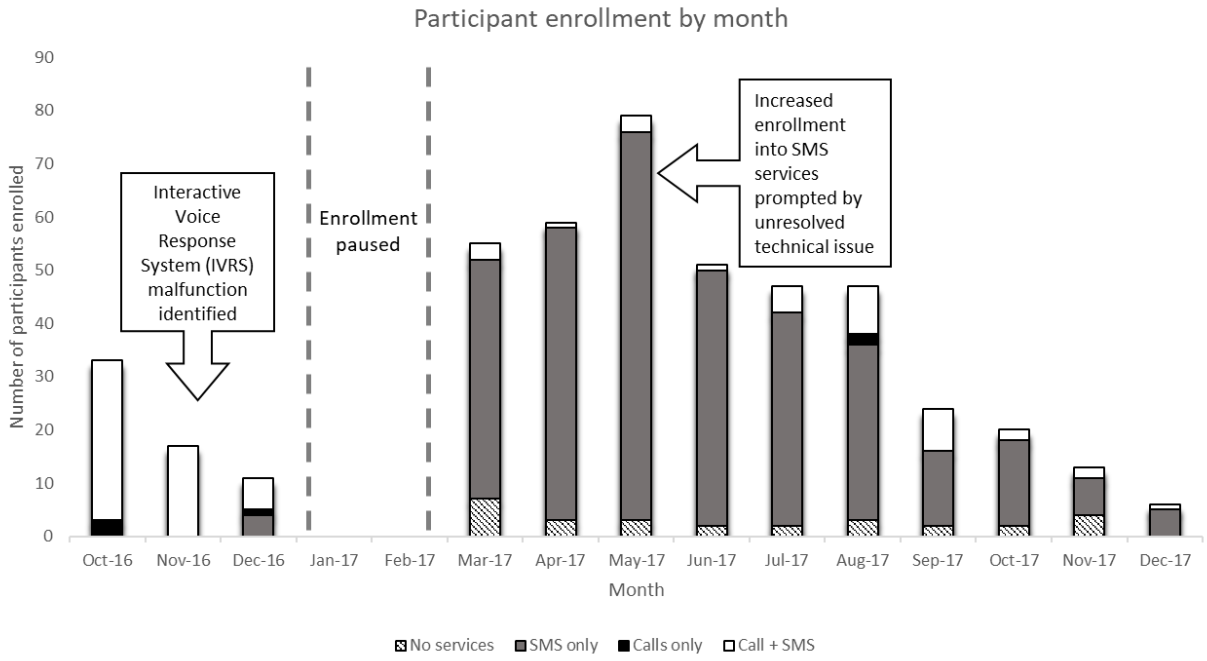

Figure 2. Participant enrollment by month and type of intervention received

On average, study participants received contact (voice call or SMS) from the Connect for Life system on 34 separate days throughout their time on the study (min=0 and max=358 days). During the study, the Connect for Life system sent participants a total of 8,234 SMS messages. It also made 31,095 IVRS calls, of which 26% were answered. **Table 2** outlines the frequency of contact, the delivery methods used (voice or SMS), and service types that participants received. The intervention delivery is further described in a separate process evaluation paper.[40]

Table 2. Intervention level and type received by study participants (N=462).

Intervention Exposure Measure		N	%
Number of days of Contact	None	28	6.06%
	Low (12-47 days of contact)	297	64.29%
	Medium (48-95 days of contact)	53	11.47%
	High (96+ days of contact)	84	18.18%
Number of calendar quarters with Contact	None	28	6.06%
	1 quarter	7	1.52%
	2 quarters	60	12.99%
	3 quarters	145	31.19%
	4+ quarters	222	48.05%

	None	28	6.06%
	SMS only	340	73.59%
	Voice only	6	1.30%
Voice or SMS service	SMS + Voice	88	19.05%
	None	28	6.06%
	Visit reminders only	340	73.59%
	Visit reminders + pill reminders	25	5.41%
	Visit reminders + health tips	8	1.73%
Type of treatment support received	Visit reminders + health tips + pill reminders	61	13.20%

Clinical and Adherence Outcomes

ART experience & Baseline adherence: At the time of enrollment, 83.8% (387/462) of participants had been taking ART for 6 months or more, 6.5% (30/462) had been on ART for 30 days-6 months, and 9.7% (45/462) were either treatment naïve or on ART for less than 30 days at enrollment.

At baseline among participants on ART for 30 days or more, perfect adherence of 100% of doses taken in the last 30 days was reported by 50.7% (208/410) of the participants, adherence of 95% to 99% of doses was reported by 27.3% (112/410), adherence of 90% to 94% was reported by 13.2% (54/410), and adherence of <90% was reported by 8.7% (36/410).

Retention, Mortality, and Treatment Failure: Retention on ART at the 48-week study visit was 91.1% (421/462) and an additional 0.6% (3/462) of participants voluntarily withdrew from the study but continued receiving HIV care at the study site. Throughout the study 3.9% (18/462) became lost to follow-up, and 3.7% (17/462) transferred care to another clinic (**Figure 1**).

Clinicians changed the ART regimens of two participants due to treatment failure, the first of whom was treatment naïve and presented with opportunistic infections (PCP and TB) at the time of enrollment, and the second who was treatment experienced and reported poor ART adherence. Furthermore, three participants died during the course of the study, one death was due to an AIDS-

related illness (cryptococcal meningitis), while one death was caused by a myocardial infarction, and the final participant's cause of death was not reported.

Table 3 describes the key outcomes of the cohort at each study visit and includes all available measurements at each time point.

Table 3. Primary and secondary outcomes by study visit*

	Baseline (N=462)	**12 week (N=454)**	**24 week (N=430)**	**48 week (N=421)**
Adherence ≥95%	320/410 (78.05)	295/333 (88.59)	339/388 (87.37)	355/393 (90.33)
Treatment naïve (<30 days)	n/a	31/32 (96.88)	34/36 (94.44)	35/35 (100.00)
30 days – 6 months on ART	27/30 (90.00)	20/23 (86.96)	22/24 (91.67)	24/27 (88.89)
>6 months on ART	293/380 (77.11)	244/278 (87.77)	283/328 (86.28)	296/331 (89.43)
Adherence >95% IIT (Includes LTFU and died pts as nonadherent)	320/410 (78.05)	295/337 (87.54)	339/401 (84.54)	355/414 (85.75)
VL Suppression cumulative**	262/283 (92.58)	279/299 (93.31)	294/318 (92.45)	335/364 (92.03)
VL Suppression (per VL done at each study visit)	262/283 (92.58)	50/53 (94.34)	72/81 (88.89)	162/178 (91.01)
Knowledge Score (mean)	85%	86%	87%	88%
Knowledge >90%	173/458 (37.77)	142/330 (43.03)	166/386 (43.01)	182/378 (48.15)
Quality of Life (mean, max score 120)	88.31	89.41	89.97	88.39
High QOL (≥90)	194/426 (45.54)	150/298 (50.34)	181/358 (50.56)	199/381 (52.23)
Died (cumulative)	n/a	1/462 (0.22)	3/462 (0.65)	3/462 (0.65)
Lost to Follow-Up (cumulative)	n/a	3/462 (0.65)	10/462 (2.16)	18/462 (3.90)

**Denominators vary based on number of participants who completed each survey instrument at each visit, variance is due to missed visits or forms not completed. The N reported in each column reflects total number of people remaining enrolled in the study at each time point, while the denominator in each row reflects the number of data points collected for each variable. **Viral load at baseline is recorded for participants that had a viral load test result on file for taken at that visit or within the 6 months prior. As VL testing is conducted annually, in this table the last VL outcome is carried forward to visits where no VL was taken in order to represent the overall VL coverage and suppression rate for the cohort.*

Adherence: The 462 participants reported a total of 1,540 adherence observations. The proportion of participants with ≥95% adherence improved from 78.0% (95% CI 74.4-82.4%) at baseline to 90.3% (95% CI 87.0-93.1%) at 48 weeks. Among treatment experienced participants, there is strong evidence of an improvement in adherence, with an increase from 77.1% (293/380) at baseline to 89.4% (269/331) at the final visit (McNemar's test = 21.88, P<0.001). Participants who were adherent at the

time of enrollment continued to have higher adherence at subsequent visits, and adherence was not associated with intervention exposure level (**Figure 3**).

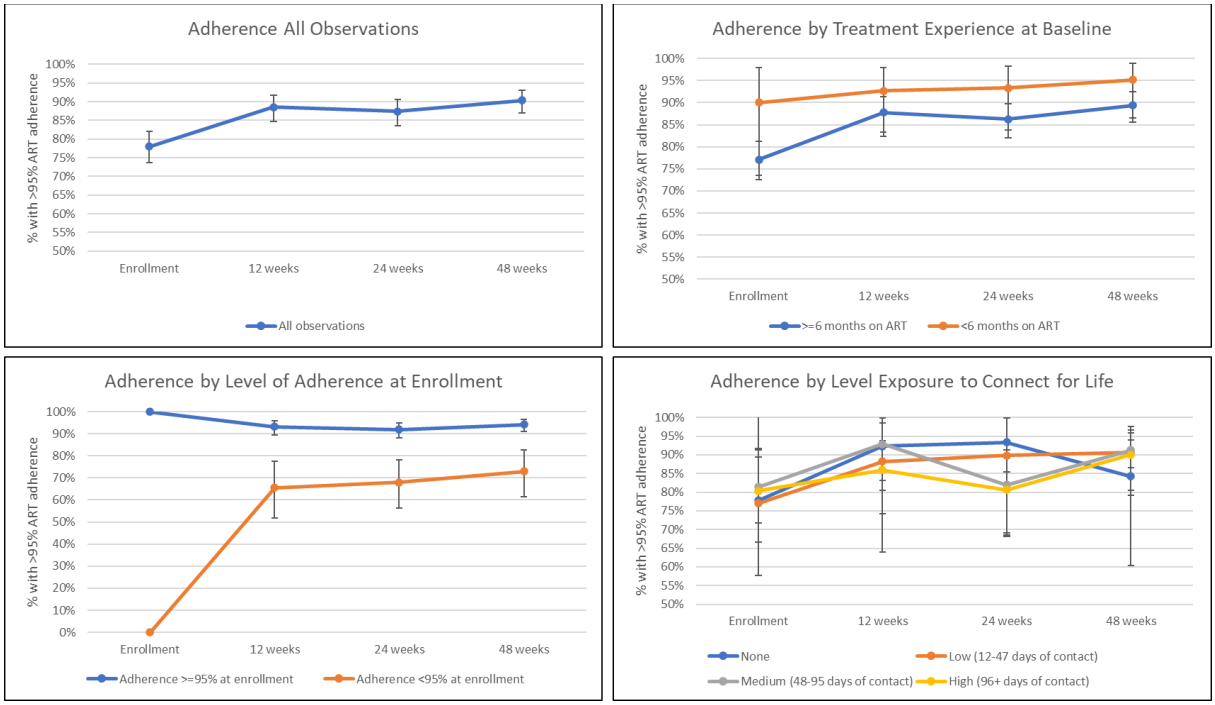

Figure 3. Adherence per study visit (includes all available data points at each study visit)

VL suppression: There were 595 routine viral load test results recorded for 374 participants. Of these, 47.6% (283/595) were recorded at the baseline visit and 52.4% (312/595) at subsequent visits (**Figure 4**). There was no change in suppression rates from baseline to end of study among treatment experienced participants, and viral load suppression was not associated with intervention exposure level.

Viral load coverage was low, especially among the participants who were new on treatment at study enrollment. The proportion of participants who had at least one VL test done at any visit (viral load test coverage) was 81.2% (375/462) overall. However, coverage was 91.2% (353/387) among participants who were treatment experienced (≥6 months) at enrollment and only 28.0% (21/75) for participants who were new on ART (<6 months) at enrollment. Of the viral load tests done in the new

on ART group, 95.2% (20/21) of these tests were recorded at the 48-week visit, which may explain the decreased suppression rate (81.0%, 17/21) at the 48-week time point (as only one viral load, which was undetectable, was reported before this time point for this group).

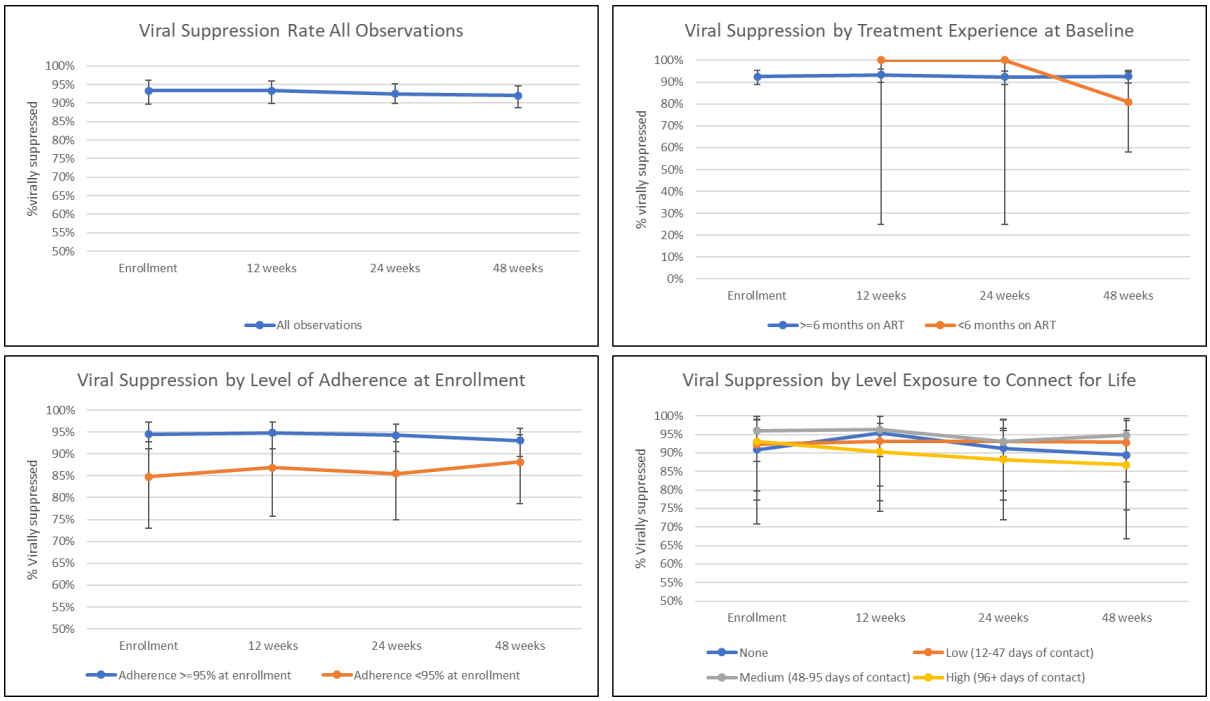

Figure 4. Viral load suppression per study visit (includes all available data points at each study visit)

Quality of Life: Among participants who were new on treatment at enrollment, the QOL score on the WHOQOL-HIV BREF scale improved from baseline to 48 weeks. Treatment experienced participants had a higher mean QOL at baseline (89.02 of a possible 120 points) than those who were new on ART (84.6, P=0.01). For the participants who were new on ART, mean QOL increased from 84.6 at baseline to 91.01 at 48 weeks (t=-2.2491, P=0.025), with the largest improvement occurring in the domain related to level of independence (mobility, activities of daily living, dependence on medication or treatments, and work capacity). There was no statistical evidence for a change in QOL for treatment experienced participants from baseline to end of study. There was no association between QOL score and level of intervention exposure.

HIV knowledge: There was a small increase in the mean knowledge score between baseline (84.5%) and 48 weeks (88.0%) (t=-4.6825, P<0.0001). There was no difference between the experienced and new participants in knowledge scores. Nearly all participants correctly answered questions regarding how HIV can be transmitted, while most incorrect answers were on questions related to clinical topics such as whether an effective HIV vaccine exists or understanding the distinction between HIV and AIDS. Exposure to the intervention did not impact the knowledge score, regardless of whether the participants did or did not receive health tips as part of the intervention.

Factors affecting adherence and viral load

The findings from multivariable models of associations between various demographic, clinical, and behavioral factors and the outcomes of adherence and viral suppression are outlined in **Table 4** and **Table 5**, respectively. Each table includes only the variables that had an association with the respective outcome of interest with a p-value <0.1 in unadjusted univariate analyses.

We found that, while adherence improved over the course of the study, there was no association between intervention exposure and adherence (aOR=1.10, 0.72, 0.64 for low, medium, and high exposure, respectively; P=0.28). Illicit drug use in the 3 months prior to enrollment was associated with nonadherence (aOR 0.56; 95% CI 0.31-1.00; CI P=0.05) Participants with optimal adherence (>95%) at baseline had higher odds of optimal adherence at follow-up (aOR 5.83; 95% CI 3.60-9.46; P<0.001).

Viral load suppression did not change over the course of the study, and there was no association between intervention exposure and viral load suppression (aOR=1.92, 4.22, 0.96 for low, medium, and high exposure, respectively; P=0.41). There was weak evidence that participants who had been on

treatment for more than 6 months at enrollment were more likely to be virally suppressed at follow-up than those who were new on treatment at enrollment (aOR=3.67; 95% CI 0.89-15.15; P=0.07).

The 69 participants who were on second-line antiretroviral regimens (indicating previous treatment failure or intolerance) were less likely to have suppressed viral load (aOR=0.33; 95% CI 0.14-0.78; P=0.01) and may also less likely to be adherent (aOR=0.76; 95% CI 0.43-1.37; P=0.37). The viral load suppression rate among these second-line patients did not improve over the course of the study. At baseline, 77.1% (95% CI 64.8-89.4%) of second-line patients had undetectable viral load measurements as per their most recent VL test; at 48 weeks this was 80.7% (95% CI 70.53-90.76%), reflecting no significant change (McNemar's test=0.00; P=1.00).

Table 4. Factors associated with self-reported optimal adherence (≥95%) assessed in a multivariable logistic regression model

		% Adherent	aOR	P-value
Intervention Exposure	None	85.14	1.00	0.28
	Low (12-47 days of contact)	86.19	1.10 (0.41-2.94)	
	Medium (48-95 days of contact)	86.74	0.72 (0.23-2.28)	
	High (96+ days of contact)	84.31	0.64 (0.22-1.87)	
Baseline Adherence	Adherence <95% at enrollment	48.17	1.00	**<0.001**
	Adherence ≥95% at enrollment	95.02	5.83 (3.60-9.46)	
	No adherence data at baseline	96.25	9.89 (2.44-40.10)	
Treatment Experience at baseline	<6 months on ART	93.24	1.00	0.37
	6+ months on ART	84.74	0.72 (0.31-1.70)	
ART Regimen	First Line	78.75	1.00	0.37
	Second/Third Line	87.31	0.76 (0.43-1.37)	
Problem Alcohol Use*	No	86.85	1.00	0.23
	Yes	80.09	0.73 (0.44-1.00)	
Any Drug Use (3 months preceding enrollment)	No	86.80	1.00	**0.05**
	Yes	78.13	0.56 (0.31-1.00)	

**Problem alcohol use defined as two or more episodes of heavy episodic or 'binge' drinking (>five drinks) in the prior month or >14 drinks per week on average.*[55,56]

Table 5. Factors associated with viral load suppression assessed in a multivariable logistic regression model

		% VL Suppressed	aOR	P-value
Intervention Exposure	None	87.80	1.00	0.41
	Low (12-47 days of contact)	92.47	1.92 (0.38-9.62)	
	Medium (48-95 days of contact)	93.10	4.22 (0.45-39.59)	
	High (96+ days of contact)	88.73	0.96 (0.15-6.10)	
Baseline Adherence	Adherence <95% at enrollment	86.89	1.00	0.80
	Adherence ≥95% at enrollment	92.98	1.14 (0.35-3.71)	
	No adherence data at baseline	94.12	2.32 (0.19-27.67)	
Treatment Experience at baseline	<6 months on ART	80.95	1.00	0.07
	6+ months on ART	92.16	3.67 (0.89-15.15)	
Baseline Viral Load	Detectable (≥50 copies/ml)	74.47	1.00	**0.01**
	Undetectable (<50 copies/ml)	89.29	0.44 (0.09-2.17)	
	No VL data at baseline	93.97	1.86 (0.42-8.24)	
Serodiscordant Relationship	Not in a relationship	90.28	1.00	0.76
	Seroconcordant relationship (both HIV+)	98.57	- (---)	
	Serodiscordant relationship (partner is HIV-)	93.27	1.12 (0.34-3.69)	
	Unknown/Did not report	90.16	0.68 (0.22-2.08)	
ART Regimen	First Line	94.12	1.00	**0.01**
	Second/Third Line	80.39	0.33 (0.14-0.78)	
Adherence (post-baseline)	Adherence <95%	84.52	1.00	0.93
	Adherence≥95%	92.84	1.07 (0.24-4.68)	

Sensitivity Analyses

Both univariable and multivariable analyses were reproduced using continuous variables for intervention exposure and adherence. The analyses were also reproduced using logistic regression and mixed effect models instead of GEE and then using an intention-to-treat approach for participants who were deceased or lost to follow-up.

For each sensitivity analysis, the direction of adjusted odds ratios did not change for any of the independent variables and the effect sizes were similar.

Discussion

Key Results

The study used a personalized mobile phone adherence intervention over a 48-week period as a vehicle to improve adherence to daily ART and viral load suppression among a cohort of participants with HIV. We observed an improvement in adherence over time, with the proportion of participants taking more than 95% of their ART doses increasing from 78.6% at baseline to 90.3% at 48 weeks. The improved adherence observed in the cohort was not attributable to exposure to the mobile phone intervention as measured by number of days with any intervention contact. This may indicate that study participation alone had a positive effect on adherence. Through study participation, participants received several elements that are not standard of care: repeated adherence measurements (on the visual analogue scale questionnaire), discussions with clinicians and study staff (especially at enrollment), and SMS visit reminders. These elements may have helped improve adherence, by increasing motivation to adhere, improving on-time attendance of appointments and thereby availability of medication, or by other mechanisms.

We found that quality of life improved in the year following ART initiation. For participants in our cohort who had been on treatment for less than 6 months at the time of enrollment, a small increase was observed in the mean quality of life score from 84.6 points (of a possible 120) at baseline to 91.01 points at 48 weeks. This improvement was not observed among treatment experienced participants, who already had a higher mean quality of life score at baseline. This supports the findings of previous studies conducted showing improved quality of life after starting or switching ART regimens.[44,57–59]

While adherence and quality of life improved, viral load suppression rates did not change significantly over the course of the study, with 92.6% of participants with a viral load done suppressed at baseline and 92.0% suppression at 48 weeks. The intervention did not have any observed effect on viral load suppression. An important finding was that the coverage of routine viral load testing was lower than expected, especially among participants who were new on treatment at baseline. Just 28.0% (21/75) of these participants had a viral load test done during the study period, while clinical guidelines required testing at 12 months on treatment (updated guidelines from 2018 now require a viral load assay at both 6 and 12 months).[60,61] Poor coverage of testing may have been attributed to challenges with eligibility under the Outpatient HIV/AIDS Treatment (OHAT) package provided by the Philippine Health Insurance Corporation (PhilHealth) to cover the cost of laboratory tests.

While self-reported adherence was lower in ART experienced participants, their viral load suppression rates were still higher than participants who were new on ART at baseline. The lower viral suppression rate (81.0%) among the new on ART participants is not fully explained through poor adherence. This indicates the importance of monitoring drug resistance, which occurs at higher than expected rates in the Philippines.[62,63] Furthermore, there should be an emphasis on accelerating the use of new, more effective first-line antiretroviral regimens which may achieve faster viral suppression in patients starting ART.

The findings also highlight the need for a differentiated approach to adherence support, with a strong focus on becoming undetectable for new patients (e.g., “Undetectable=Untransmissible”/“U=U” messaging) as well as resistance monitoring. Among more experienced patients, there should be a focus on addressing treatment fatigue. People on second-line therapy may require more intensive adherence support as we found that they continue to have poorer adherence and viral load suppression than those on first-line regimens.

Social and family support remain important factors in successful adherence and treatment outcomes. [64,65] A substudy of 193 participants from this cohort found high rates of depression (21.8%) and anxiety (37.3%) among the cohort. However, the substudy found that these mental health factors did not impact ART adherence after factoring in low social and family support.[66] The proportion of participants in our cohort who confirmed they had disclosed their HIV status to family or friends was very low at just 31.6%.

Another group requiring attention is people who use illicit drugs. An earlier analysis of risk factors in this cohort [67] found that injection drug use (aOR=0.54, P=0.090) and inconsistent condom use (aOR=0.50, P=0.103) were both potentially associated with reduced adherence to ART. Indicating that these groups may be at risk of poor clinical outcomes as well as further HIV transmission to their sexual contacts. Study participants used drugs and alcohol at rates five- to 10-fold higher than the general population of the Philippines. Methamphetamine use is strongly associated with high-risk sexual behavior and HIV acquisition,[68] and is commonly used by MSM in chemsex or 'Partee 'n' Play' activities. Compounding these risks, evidence-based HIV prevention is not widely available in the Philippines – condom distribution has been restricted,[69,70] and pre- and post-exposure prophylaxis services are only available in select geographic areas (mostly large cities).[71,72]

In the absence of social and family support and in the context of substance use, mHealth platforms provide a mechanism for participants to be reminded about the importance of their treatment and to have more frequent contact with their healthcare providers.

Effectiveness of the Intervention

It is difficult to draw conclusions about the effectiveness of the mobile health intervention due to the poor fidelity of the intervention delivery. We found in the process evaluation that acceptability of the

intervention was high, and that the personalizable aspect of the intervention, i.e. the ability to select the desired type of and frequency of contact, was important to participants. Participant feedback was most positive regarding the health tips and visit reminder services.[40]

The SHIP clinic has continued to use the Connect for Life platform after this demonstration project. The technical issues that plagued the initial rollout happened less frequently over time, leading to improved fidelity of the service delivery. At the time of publication, clinicians and participants report high levels of satisfaction with the intervention. In 2019, clinic staff conducted a retrospective analysis of clinic records for all scheduled visits between January 2017 and November 2019. The review found that patients receiving the SMS reminder service were more likely to attend their scheduled appointment on time than those who opted out of reminders (38% vs 30% on-time attendance, $F=9.00$, $p=0.0028$).

The intervention leveraging the Connect for Life platform in the Philippines setting was adapted from the same platform used for Call for Life Uganda as well as the mMitra and Treatment Advice using Mobile Alerts projects in India.[41,44] Studies in these other settings found improvement in patient outcomes among participants receiving the interventions.

The Call for Life study in Uganda found that viral load suppression was most improved among the group with moderate usage of the intervention, which is mirrored by our findings in the Philippine setting which suggest that medium exposure level (i.e., an average of one contact per week) was the most effective. A systematic review and meta-analysis of studies of mHealth interventions to support ART adherence by Shah, Watson, and Free found that it is unclear if the frequency of contact (daily, weekly, scheduled) influences intervention outcomes. However, interventions that are ‘interactive’ and use several behavior change techniques more often lead to improvements in adherence. [36]

While there has been substantial heterogeneity in results of mHealth adherence support interventions overall [36,73–76], these platforms should continue to be explored as part of differentiated care and treatment support services. In the context of the dual HIV and COVID-19 pandemics, a wider variety of services are being delivered virtually and community groups in the Philippines have advocated for the increased availability of mHealth and tele-health services for PLHIV.[77–80]

Strengths and Limitations

The involvement of end users in the intervention design and the thorough process evaluation of the Connect for Life study were strengths that provided helpful context for understanding both the process of delivering the intervention and its results.[40,45]

Owing to technical issues, only 22.1% (102/462) of the participants received the IVRS pill reminder intervention and others received a scaled-back SMS text message intervention. Following this study, the frequency of technical issues decreased significantly, and the study site has continued to provide pill reminder calls as a routine service for all new patients starting ART.

This study had several weaknesses that limit the interpretation of results. It used a quasi-experimental design, which meant that exposure to the intervention was not randomized. Moreover, the participants within each of the different intervention exposure levels received a different number of messages and days of contact, and also received different types of messages (i.e. pill reminders, health tips; calls, text messages), which may have impacted the internal validity of the study when making comparisons between the exposure groups.

The intended measurement of outcomes was affected both by the poor coverage of routine viral load testing and poor quality and completeness of non-self-reported adherence measures (pharmacy refills records and interactive SMS reports). Both loss to follow-up and elevated viral load were rare, and so the study sample was underpowered to examine factors associated with these outcomes. While

relying on self-report of adherence alone was not ideal, studies have shown that self-reported adherence is useful and does correlate with clinical outcomes.[81–83] Finally, the knowledge measurement did not specifically link questions to the material in the health tips, but rather measured general HIV knowledge. A tailored KAP questionnaire with several versions may have been a better approach.

Conclusions

This study provides an in-depth analysis of demographic, clinical, and behavioral characteristics among a cohort of MSM living with HIV in the Philippines. We found that, by the end of the study, over 90% of the cohort reported ≥95% adherence to ART and that viral suppression rates were above 90% among those who received a test. Low coverage of viral load testing and poor suppression rates among participants who were treatment naïve at enrollment require targeted intervention. PLHIV who use drugs and those on second-line treatment also require attention as they were found to be less likely to be adherent and virally suppressed, respectively.

There was no strong evidence that exposure to the mobile phone intervention conducted using the Connect for Life platform improved adherence to ART or viral load suppression. Observed improvements in adherence were not attributable to exposure to the intervention, which may be due in part to challenges in the intervention delivery during the course of the demonstration project.

Improved understanding of the factors associated with adherence and viral suppression may inform tailored prevention and treatment interventions, including those that use mHealth technologies, for MSM in the Philippines and other similar settings.

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