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TÍTULO

"Efficacy of a cell phone-based text messaging intervention in improving ART initiation, medication pick-up frequency, and retention in care amongst young adults living with HIV in Peru"

Alumnos:

Rodrigo Alonso Calderón Flores

Jeffrey Nathan Freidenson Bejar

Asesores:

Dr. Elsa Violeta González Lagos

Dr. Fernando Alonso Mejía Cordero

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JURADOS

PRESIDENTE: DR. LEANDRO HUAYANAY FALCONI

SECRETARIA: DRA. NATALÍ LEIVA REYES

VOCAL: DR. MARTÍN MONTES DELGADO

ASESORES DEL TRABAJO DE INVESTIGACIÓN

Dra. ELSA VIOLETA GONZÁLEZ LAGOS

DR. FERNANDO ALONSO MEJÍA CORDERO

DEDICATORIA

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TABLA DE CONTENIDOS

Abstract

Background: Text messaging (SMS) interventions to improve HIV retention in care have shown mixed results, probably due to the diversity of features of their design and implementation.

Methods: Using routinely collected data of the largest HIV program in Lima, we retrospectively evaluated the efficacy of an adapted single-arm, one-way SMS pilot intervention, intended to improve compliance with medical and ART pick-up appointments, by use of (i) SMS reminders before scheduled visits, (ii) a motivational SMS after scheduled visit, and (iii) phone calls after missed visits delivered for up to 9 months. The SMS group included people living with HIV (PLWH) ages 18-29 starting or restarting antiretroviral therapy (ART). For the control group, we non-randomly selected PLWH up to 35 years-old who were enrolled in the same HIV program within overlapping or closest dates to those of the SMS group (n = 320). The main outcomes, analyzed with multivariable adjusted models with follow-up closed by 18 months, were first year retention in care, ART initiation and medication pick-up frequency per three semesters.

Results: First year retention in care was 61% in both groups (aRR: 1.01 [95% CI: 0.81-1.25]; p = 0.93); ART initiation was 83% (55/66) in the SMS-group and 79% (254/320) in the control group (aHR: 1.21 [95% CI: 0.89-1.62]; p = 0.23). Median number of ART pick-up visit during the first semester was 8 (IQR: 6-9) in the SMS group and 7 (IQR: 3-8) in the control group (aRR: 1.01 [95% CI: 0.81-1.25]; p = 0.93); in the following two semesters, we found no differences between the study groups.

Conclusion: This pilot one-way SMS intervention tailored to young adult PLWH from a resource-constrained setting showed no strong effects across multiple HIV-care outcomes, all of which showed suboptimal results.

Keywords: HIV infection, retention in care, mHealth, SMS one-way intervention, Peru

Resumen

Introducción: Las intervenciones con mensajes de texto (SMS) para mejorar la retención en cuidado de pacientes con VIH han presentado resultados heterogéneos, probablemente por las diversas características a la hora de diseñarlas e implementarlas.

Métodos: Usando datos recolectados de manera rutinaria en el programa de VIH con más pacientes en Lima, evaluamos retrospectivamente la eficacia de una intervención piloto de SMS de plataforma unidireccional en una cohorte de un brazo. Esta buscó mejorar la adherencia a citas médicas y de recojo de terapia antiretroviral (TARV), usando (i) SMS recordatorios antes de las citas agendadas, (ii) SMS motivacionales luego de una cita acudida, y (iii) llamadas telefónicas luego de una cita no acudida; enviados hasta por 9 meses. El grupo SMS incluyó a personas que viven con el virus del VIH/SIDA (PVVS) que tenían una edad de 18-29 años y que iniciaban o reiniciaban TARV. Para el grupo control, seleccionamos a PVVS hasta 35 años de edad que fueron enrolados al programa de VIH con fechas que coincidían o eran cercanas a las del grupo SMS (n = 320). Los objetivos principales, analizados con modelos ajustados multivariados con un seguimiento de 18 meses, fueron retención en cuidado durante el primer año, inicio de TARV, y frecuencia de recojo de terapia por 3 semestres.

Resultados: La retención en cuidado durante el primer año fue de 61% en ambos grupos (RRa: 1.01 [95% IC: 0.81-1.25]; p = 0.93; el inicio de TARV fue de 83% (55/66) en el grupo SMS y 79% (254/320) en el grupo control (HRa: 1.21 [95% IC: 0.89-1.62]; p = 0.23). La mediana de visitas a recojo de TARV durante el primer semestre fue de 8 (RIC: 6-9) en el grupo SMS y 7 (RIC: 3-8) en el grupo control (RRa: 1.01 [95% CI: 0.81-1.25]; p = 0.93); en los siguientes dos semestres, no encontramos diferencias entre los grupos de estudio.

Conclusión: La intervención piloto de SMS unidireccional diseñada para adultos jóvenes con VIH de un contexto con recursos limitados no mostró efectos relevantes en múltiples indicadores del cuidado de pacientes con VIH, indicadores que además mostraron resultados sub-óptimos globales.

Palabras clave: Infección por VIH, Retención en cuidado, mHealth, Intervención con SMS, Perú

Introduction

In response to the global need of strengthening Human Immunodeficiency Virus (HIV) control, different Short Message Service (SMS)-based interventions have been proposed to improve adherence to antiretroviral therapy (ART) and retention in care [1,2]. These two dynamic, complex phenomena are affected by factors at individual, interpersonal (patient-provider) and health-system levels [3-5].

The flexibility of SMS in terms of format, delivery and contents have contributed to the roll-out of SMS-based health interventions [6-8], sometimes with little elaboration on the specific mechanisms of action. SMS contents may contribute to behavior change [9-13], but recipients' traits such as sex, age, education, personality and/or perceptions modulate their effects [14,15]. This situation probably explains the conflicting results regarding the reported effectiveness of SMS-based interventions [16,17]

Since HIV requires lifelong care, the scale-up of SMS interventions should consider the dynamics of their effects including the residual effects, or those that remain once the delivery of the intervention ceased. Though the evidence is limited for HIV [8, 18-26], the residual effects of SMS interventions seem to decrease to pre-intervention levels for other health conditions less dependent on programmatic care [23,25,26].

In Peru, people living with HIV (PLWH) and health providers have expressed favorable attitudes toward SMS-based HIV-care interventions [27-31]. At our study center, an intervention designed and tested in the United States [32] was locally adapted (Estemos en Contacto, EEC from now on) in 2016 to improve compliance with medical and ART pick-up appointments among young-adult PLWH; the local research initially evaluated the acceptability and feasibility of the pilot SMS intervention [33]. In this study, we analyze its effectiveness through three outcomes: ART initiation, ART pick-up frequency for three consecutive semesters, and retention in care by the end of the first year of follow-up. The outcomes were compared between the SMS group and a retrospectively selected control group, similar in age and dates of enrolment to the HIV program.

Materials and Methods

Study Design

Secondary data analysis under the model of a retrospective cohort study with up to 18 months of follow-up. Our exposure was the SMS intervention considered in the original single-arm pilot cohort study (SIDISI 66351), and we retrospectively selected a concurrent control group.

Study Setting

The study center hosts the largest HIV program in Peru. The National HIV Program (NHP) procedures are regulated by national guidelines. At enrollment, nurses register sociodemographic data and provide counseling and HIV-related information. During the study period, the guidelines mandated multidisciplinary team evaluations and laboratory testing (CD4/viral load) before antiretroviral therapy (ART) initiation, with first line ART consisting of a triple single daily dose (Emtricitabine, Tenofovir and Efavirenz) [34].

After ART start, PLWH pick-up the drugs at the National Health Program (NHP) offices according to schedules indicated by nurses: at seven-days intervals during the first month and then every four weeks for approximately 70% of PLWH; the other 30% comprises individualized schedules, either with less frequent visits for PLWH working/living out of Lima -the city in which EEC was conducted-, and more frequent for PLWH who repeatedly miss such scheduled visits. ART and CD4/viral load tests are free of charge, but other lab tests and medical visits are out-of-pocket expenses for PLWH without public health insurance.

The data from these procedures, including baseline information and dates of ART pick-up visits, are registered, first in non-electronic medical records and then into the HIV program database.

Description of the SMS intervention

Implemented at the study center between November 2016 and October 2017, the one-way SMS pilot intervention aimed at improving compliance with medical and ART pick-up appointments among young-adult PLWH and consisted of: (i) reminder SMS prior to scheduled appointments with health providers for CD4 and viral load testing or ART pick-up; (ii) motivational SMS after completed visits and (iii) phone calls following missed visits [33]. Two research nurses, also staff of the NHP, and one research

assistant implemented the intervention, whose delivery occurred from the date of recruitment until the last participant reached six-months of follow-up [33].

Study population

SMS intervention group

Eligible participants were PLWH aged 18-29 years enrolled into the HIV program, either as new cases or after ART abandonment. For those willing to participate, the only exclusion criterion was the lack of a cell phone. According to data from the original study, 80 out of 98 PLWH (82%) potential eligible participants enrolled into the HIV program were recruited between November 7th 2016 and February 17th 2017.

Control group

Eligible participants for our retrospectively, non-randomly selected control group were PLWH aged 18-35 years, who became enrolled in the same NHP within dates overlapping or closest to those of the recruitment period of the SMS group. The use of similar criteria to those of the original study served to minimize bias, and the minor increase in the age eligibility allowed to minimize differences in dates of enrollment between both groups. We could not exclude PLWH without cell phones or who had refused to participate in the EEC study intervention (n = 12), because such data was absent.

Study definitions

The start of the study follow-up was the NHP enrollment date. Acquired Immunodeficiency Syndrome (AIDS) status at baseline was defined by CD4 < 200 cells/cm^3 or a missing baseline CD4 value [35]; viral suppression by a viral load ≤50 copies/ml. Retention in care was defined by at least two infectious disease outpatient visits, occurring 90 days apart during a 12-month period since the start of follow-up [36]. Non-scheduled gaps in ART pick-up visits served to define ART abandonment if exceeding 30 days, and loss to follow-up if exceeding 60 days [37].

Data management

To identify our study population, we extracted an initial data set from the routine NHP database containing de-identified basic demographic information of PLWH who were enrolled in 2016 and 2017. Then, we applied our eligibility criteria, and we cross-checked this data with the SMS-intervention database to prevent misclassification of study groups. Once completed this process, we had a unique dataset with our two study groups.

With the study population identified, we extracted baseline and follow-up general and clinical data from the NHP database: age, sex, pregnancy status, self-reported sexual orientation, marital status, level of education, CD4 and viral load. For additional data extraction from hospital data bases we used individual medical records' numerical codes. Such data included: date of ART initiation, dates of ART pick-up visits, CD4 and viral load values, vital status, date of last contact. We retrieved the data for infectious disease outpatient visits and hospitalization events from the study center's unit of informatics and statistics databases. With the original data set from the SMS intervention we determined, per participant, the time of the intervention's delivery. Two researchers (RC & EG) independently merged the data using the individual medical record code. Discrepancies on unmatched registries were solved by reviewing non-electronic records.

For data quality control, we verified 20% of the registries to ensure correct transcription from non-electronic medical records to the NHP electronic database. The final study database did not keep identifiers to guarantee confidentiality.

Sample size and statistical analysis

Based on local data [38], we expected a retention in care rate of 70% for the control group and 85% for the fixed sample size SMS group (n=80). Thus, with a study power of 80%, the estimated sample size of the control group was 292. To potentially overcome the loss of power due to missing data, the final sample size was 320.

In the main analysis, we compared three outcomes: (i) first year retention in care, (ii) time to ART initiation, and (ii) number of ART pick-up visits per each of three semesters. All time-dependent outcomes were measured since the start of the study follow-up. As this was defined by date of enrollment in the

HIV program, not the date of recruitment for the SMS intervention, we described the median of such interval.

For the estimation of hazard ratios for time to ART initiation, we performed a Cox regression analysis and censored the PLWH at the date of death or at the last day of follow-up if ART initiation had not occurred. The proportional hazards assumption was tested by graphic examination of the log-log cumulative hazard vs time and by Schoenfeld residuals. For the estimation of risk ratios of retention in care and the mean ART pick-up visits ratio per period, we performed Poisson regression models with and without robust variances, respectively. We also analyzed time to loss to follow-up with Cox regression analysis, and first-year viral suppression; for the latter, we compared risk ratios with Poisson regression models with robust variances. Moreover, as the intervention had sent reminders for viral load tests, we considered two approaches: using only the actual viral load values and assuming a detectable viral load for cases with missing values [39].

For the adjustment of all models, we included the baseline variables that had a 5% difference between both groups. For baseline CD4 and viral load values, we used the closest measurements to the start of follow-up within a +/- 90-day period. Significance for all analysis was set at $p < 0.05$ with a 95% confidence interval. We tested data assumptions of all analyses, and report deviations from such assumptions.

Data management, sample size estimation and statistical analyses were performed with Stata version 15.0 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC, licence: Universidad Peruana Cayetano Heredia).

Ethical considerations

The study protocol received approval and informed consent waiver from the Institutional Review Boards (IRB) of Universidad Peruana Cayetano Heredia and the study center. The study was conducted following the guidelines for collection, storage and use of data in health-related research from the “International Ethical Guidelines for Health-related Research Involving Humans” prepared by the Council for International Organizations of Medical Sciences (CIOMS) [40].

Results

Sample characteristics

Among the 80 participants of the SMS intervention, 14 had been actually enrolled in the HIV program long before the date of recruitment, with July 2007 as the earliest date. Therefore, to prevent bias regarding temporal differences, we excluded these 14 participants from our analysis. By doing so, the earliest dates of enrolment in the HIV program were August 8th, 2016 (SMS group) and August 13th, 2016 (control group).

The study population was predominantly male (86% in the SMS group, 83% in the control group) and the control group had older median age (27.0), which was expected due to the age eligibility criteria. At baseline, differences over 5% between both groups were observed for AIDS status, educational level, pregnancy, initial ART scheme, and missing CD4 and viral load values (Table 1).

Table 1. Comparison of baseline characteristics by study groups

Characteristics		SMS group (n= 66) N (%)	Control group (n= 320) N (%)	p value
Sex				0.48
	Male	57 (86%)	265 (83%)	
	Female	9 (14%)	55 (17%)	
Age*		25.2 (22.1-27.0)	27.0 (23.6-30.8)	<0.01
Body Mass Index (BMI*)		23.7 (21.8-26.0)	23.5 (21.6-25.7)	0.98
CD4 count†		343.5 (192-492)	289 (119-455)	0.09
AIDS†		20 (30%)	139 (43%)	0.05
Viral suppression†		4 (6%)	13 (4%)	0.64
Sexual orientation				0.81
	Heterosexual	23 (35%)	124 (39%)	
	Homosexual	29 (44%)	129 (41%)	
	Bisexual	14 (21%)	64 (20%)	
Educational level				0.08
	Primary	5 (8%)	8 (3%)	
	Secondary	31 (48%)	131 (43%)	
	Higher	29 (44%)	166 (54%)	
Women pregnant at start of follow-up				0.38
	Yes	4 (44%)	16 (29%)	
Marital status				0.92
	Married/Cohabiting	11 (17%)	59 (19%)	
	Divorced/Separated	0 (0%)	2 (0.6%)	
	Widowed	0 (0%)	1 (0.4%)	
	Single	55 (83%)	255 (80%)	
ART-naive		66 (100%)	320 (100%)	0.99
Initial ART[a]				

	1st Line scheme	33 (60%)	130 (51%)	0.24
Hospitalization events[b]				
	Yes	3 (5%)	32 (10%)	0.16

* Median (interquartile range)

† In the SMS group, missing data for CD4 count was 9% and for viral load basal values 12%; in the control group, it was 15% and 18%. Missing CD4 values were considered as AIDS positive status; and missing viral load values as not being virally suppressed.

a First-line therapy consists of: 1) Efavirenz (600mg) + Emtricitabine (200mg) + Tenofovir (300mg) or 2) Tenofovir (300mg) + Lamivudine (150mg) + Efavirenz (600mg).

[b] Hospitalization events during study follow-up.

The median number of days between dates of NHP enrollment and intervention recruitment was 0 (interquartile range [IQR]: 0-5). The median time of delivery of the intervention was 6.6 months (IQR: 5.8 – 8.0). During follow-up, the number of deaths was 2 (3%) in the SMS group and 12 (3.8%) in the control group, including two PLWH with unknown dates of death.

Outcomes

First-year retention in care rate (61%) was similar for both groups (table 2), without statistically significant differences after adjusted regression analysis (aRR: 1.01 [95% CI: 0.81-1.25]).

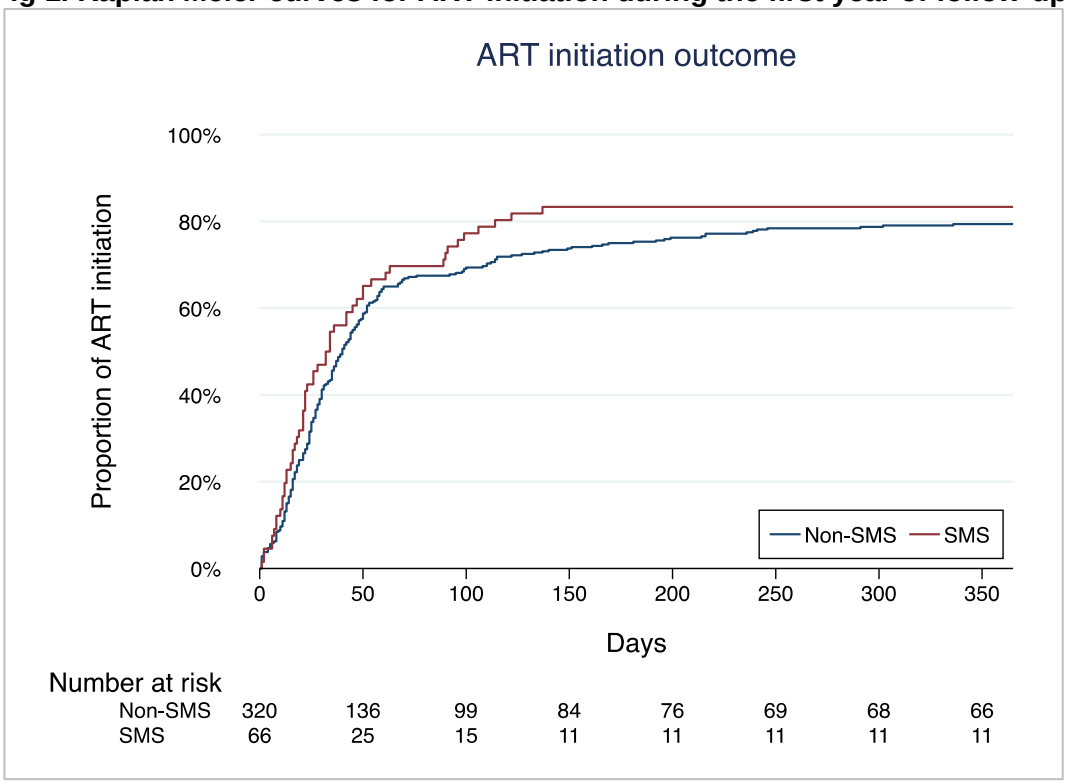
Compared to the control group, more PLWH in the SMS group initiated ART (83% vs 79%); the median number of days until ART initiation was lower, without significant differences, in the SMS-group compared to the control group (23 days vs 30 days, aHR: 1.20 [95% CI: 0.89-1.62]). (Table 2, Fig 1). This HR must be interpreted as an averaged effect as the proportional hazards assumption was not met. Linearity assumption was met as all covariates are categorical variables.

Table 2. Comparison of primary and secondary outcomes by study groups.

Outcomes[o]	Study groups		Unadjusted effect size (95% CI) †	p value	Adjusted effect size (95% CI) †	p value
	SMS (n = 66)	Control (n = 320)				
	no. (%)					
Primary outcomes						
Retention in care	40 (61%)	195 (61%)	0.99 (0.80-1.23)	0.96	1.01 (0.81-1.25)	0.93
ART initiation[a]	55 (83%)	254 (79%)	1.21 (0.90-1.61)	0.21	1.20 (0.89-1.62)	0.23
ART pick-up visits*						
First semester	8 (6-9)	7 (3-8)	1.12 (0.98-1.28)	0.09	1.12 (0.98-1.28)	0.11
Second semester	6 (6-7)	6 (6-6)	0.99 (0.90-1.09)	0.85	1.00 (0.91-1.09)	0.94
Third semester	6 (5-6)	6 (5-6)	0.99 (0.91-1.08)	0.90	1.01 (0.93-1.10)	0.83
Secondary outcomes						
Viral suppression at 1st year	29 (44%)	133 (42%)	1.06 (0.78-1.43)	0.72	1.04 (0.77-1.40)	0.80
Viral suppression at 1st year[#]	29 (73%)	133 (81%)	0.90 (0.73-1.10)	0.31	0.92 (0.75-1.13)	0.43
Loss to follow-up[a]	31 (47%)	144 (45%)	1.01 (0.69-1.49)	0.95	0.97 (0.65-1.45)	0.89

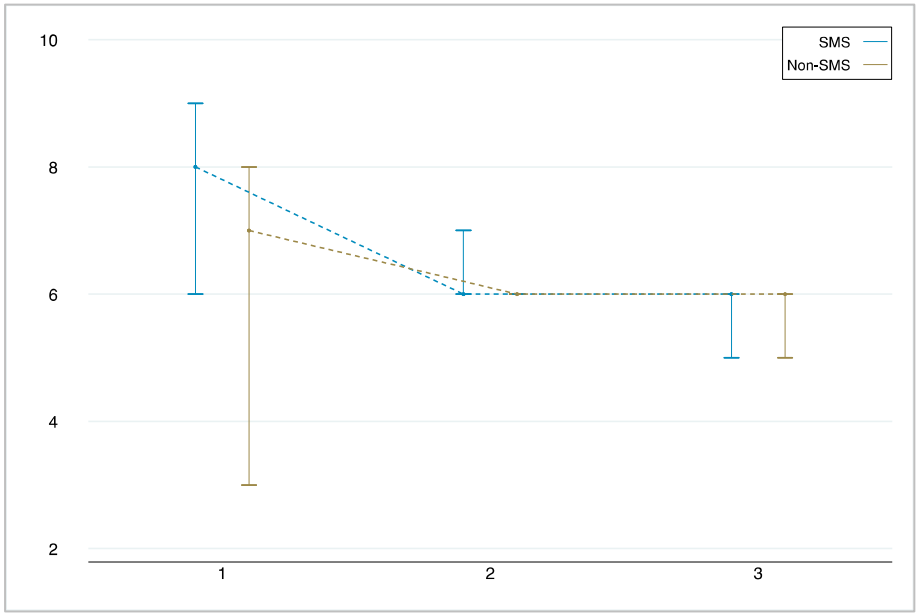
†Effect sizes were assessed as risk ratios (SMS group/Control group). Adjusted analyses on all outcomes included the following baseline covariates: AIDS status, education level and pregnancy.
* Median (interquartile range)
[a] Hazard ratios
[o] All adjusted regression analyses assumed subjects had AIDS at baseline if CD4 count value was missing.
[#] This regression model used only subjects with available viral load values and basal CD4 count values.

Fig 1. Kaplan Meier curves for ART initiation during the first year of follow-up.



The median number of ART pick-up visits in the first semester was 8 [IQR: 6-9] in the SMS-group and 7 [IQR: 3-8] in the control group. In the following two semesters, the median was 6 for both groups, without significant differences after adjusted regression analysis (Table 2, Fig 2).

Fig 2. Median and interquartile range of ART-pickup visits per participant by follow-up semester



Note: Non-SMS group had a median of 6 IQR [6-6] visits during the second semester.

Missing viral load values for first year viral suppression were lower in the SMS group (39%) than in the control group (48.4%). Based on available values only, first year viral suppression was not significantly lower in the SMS group compared to the control group (73% vs 81%, aRR: 0.92 [CI 95: 0.75-1.13]). However, when assuming first year missing viral load values as non-virally suppression (and missing CD4 basal values as AIDS status), we observed similar first-year viral suppression rates (44% vs 42%; aRR: 1.04 [95% CI: 0.77-1.40]).

There were no differences in first year loss to follow-up (47% in the SMS group vs 45% in the control group; aRR: 0.97 [CI 95: 0.65-1.45]). The outcomes' analyses considering only the available basal CD4 values did not alter these results (Supplementary Table 1).

Discussion

In this study, the local SMS based intervention tailored to young-adult PLWH showed no strong benefits for selected HIV care outcomes.

Because youth [41] and socioeconomic constraints [42] are markedly associated with missed appointments, the local SMS intervention was implemented at a public hospital serving mostly low socio-economic groups, with a study population of predominantly young, male PLWH. However, retention in care and viral suppression were suboptimal for both study groups. During the 2006-2012 period, retention rates at our study site were 60% [38]; the lack of major progress within a four-year period highlights the local gaps in HIV control. The average attrition incidence, or treatment abandonments during the first year of follow-up of this study was 66 per 100 person-years, which contrasts with the 8 per 100 person-years reported in another study with a similar SMS-intervention approach [37]. Additionally, viral suppression rates during the first year of follow-up were approximately 43%, a value close to the 42% reported by the Peruvian HIV national program in 2018 [43].

In parallel to the implementation of the local SMS intervention, other studies of SMS interventions were published, providing a better understanding of the interplay of factors which, at the stages of design, delivery, and post implementation, influence on the effectiveness of SMS-based interventions. With publications of SMS interventions without major effectiveness, the results of most recent research sometimes differed from earlier work [44-49]. Overall, the findings of such recent research pointed to increased effectiveness of interventions that targeted specific subgroups, implemented customized SMS contents and two-way platforms [50], which also facilitate customization [51]. According to a 2017 systematic review, incentives such as money or free phones were considered in 50% of mHealth interventions for HIV care [46]. Based on this emerging evidence, the delivery of the local SMS intervention through a one-way platform without additional incentives to the participants may have limited the intervention's effectiveness.

In 2019, a meta-analysis of randomized controlled trials (RCT) showed no impact of one-way SMS on HIV appointment adherence [49]; yet one of the four studies showed a post-hoc benefit in

retention in care for urban PLWH who had recently initiated ART (HR: 0.20, [95% CI: 0.06-0.64]; p = 0.006). In that study, the formative research-based SMS were sent before and after an appointment, with additional educational monthly SMS [37]. In a SMS program implemented in a real routine setting, which combined reminder and motivational SMS, the better effects corresponded to messages targeted to key subpopulations, such as PLWH with suboptimal ART adherence [52]. At a sexually transmitted infections private consultation clinic in Peru, thus probably serving higher socio-economic groups, a SMS intervention targeted to PLWH with history of missed appointments contributed to increase appointment adherence by 20% compared to a non-intervened group [53].

In 2017, a meta-analysis of seven studies concluded that SMS reminders reduced appointment non-attendance (OR: 0.66; 95% CI: 0.48–0.92) [54]. The three studies with significant effects were targeted to HIV pregnant women [55], caregivers of children exposed to HIV [56], and non-adherent PLWH with substance use [51]; in contrast, the four studies without significant effects were not targeted to specific groups and used SMS contents as generic reminders [57-60]. In the study with greater effects, the intervention considered additional features, such as a two-way platform, free cellphones, daily queries on multiple risk factors, and contents designed by the participants.

The RCT in 6 US HIV clinics that served as groundwork for this intervention reported retention in care 22% higher in the intervened group compared to the control group (RR: 1.22; [95% CI: 1.09-1.36]). However, sub-group analysis showed a lower and non-significant effect for young-adult PLWH aged 18-39 years (RR: 1.08; [95% CI: 0.89-1.32]) and for PLWH with at least one unmet social need (RR: 1.04; [95% CI: 0.88-1.21] [32]. Thus, the current evidence supports the approach of identifying potential subgroups of PLWH that could benefit more from the SMS to guide the use of these interventions. Even if the local SMS intervention was targeted to young PLWH recently enrolled in an HIV program, perhaps there was higher heterogeneity than expected within a study group that included low-educated, married pregnant women and single individuals with university education.

In terms of customization, the local SMS intervention tried to individualize the messages to connect with users. Leveraging on previous local experience that showed preference for motivational,

concise, and simple messages, the SMS were mostly motivational, sometimes with a spiritual tone [29]. Validation of the messages' contents of the local intervention occurred before the implementation, with input from local health providers and PLWH. As the level of customization was mostly restricted to the first phases, it may have not been enough to sustain the desired effect. In the previously mentioned RCT with high effectiveness [51], the SMS contents had a high level of customization facilitated by the two-way platform. The participants relied on messages they had created anticipating different contingencies, with contents occasionally including intimate topics, such as family and religion, and even codewords for specific instances.

The effects of intervention can also vary in time, during its delivery and afterwards [8,51]. Although the differences were minor and not statistically significant, our intervention group had higher frequency of ART initiation and higher number of ART-pick up visits in the first semester; the latter finding was not sustained afterwards. These findings suggest higher effectiveness of the intervention at initial stages. The variability of effects during the delivery of the intervention could relate to a higher initial engagement and receptiveness to health providers' messages, particularly due to the use of motivational contents; however, such engagement could wane. Moreover, if any sense of novelty contributed to the effectiveness reported ten years ago with the first SMS trials, it may have also diminished [44,45,61].

The dynamics of the residual effects of SMS-based interventions, including potential negative effects, should be thoroughly considered because HIV requires lifelong care. After two years of a SMS intervention which fostered internalizing adherence as a habit, the removal of the intervention affected the outcomes of the less resilient participants, who were more dependent on the intervention [62]. In our study, the variation in the number of ART-pick up visits between the first and second semester of follow-up seemed more pronounced for the SMS group which raises the possibility of disadvantages after its cease and reinforces the complexity of the dynamics of the intervention effects in time. Relatedly, heterogeneity in the intervention's delivery, particularly in routine settings, may be expected. In the study that was adapted for this intervention, which additionally considered forging a connection with the health provider, face-to-face encounters at clinic visits and interim calls, telephone calls were used at 7 and 2 days before a scheduled visit and the day afterwards; the authors reported 47% successful phone calls.

Even a highly effective SMS intervention, fully implemented and delivered as part of routine services of the HIV program, would not by itself reverse the suboptimal HIV care outcomes here reported. By posing barriers to access treatment, structural factors may affect such outcomes potentially hindering the intervention's efficacy- besides messaging content and individual characteristics. During the study period, PLWH had to undergo multiple consultations before starting ART; however, administrative systems sometimes allowed one appointment per day, increasing the hurdles for going to the hospital (long waiting queues for appointments, unpaid absence from work, especially if employers do not know about the patients' HIV status, as too often is the norm; long commuting; etc.). Therefore, it is crucial to also address these structural barriers to improve HIV care outcomes and interventions' efficacy.

Strengths and limitations of the study

The major limitation is that we assumed the delivery of the intervention as planned; this implied that, similarly to other SMS interventions with one-way platforms, we also assumed that participants had read the SMS. Future sub-analyses should adjust for the actual degree of delivery of intervention.

We selected a control group in ways intended to minimize bias. Precisely to reduce temporal bias, we excluded 14 participants from the SMS group, even if such decision may have underpowered our final analyses. The measurement of outcomes, though retrospective, relied on routinely gathered data under systematic procedures at the study site with extensive data cleaning to minimize data errors. Considering that the intervention aimed to improve appointment adherence, the comparison of non-missed scheduled appointments between both study groups would have been ideal but it was not feasible in the absence of such data for the control group. Finally, our retention rates strictly illustrate the continuity of care at the study center, as we could not track if PLWH had decided to receive care elsewhere.

Despite these limitations, the trends with our findings are consistent pointing to the absence of major effects. At a time that increases the demand for mHealth, our study contributes with relevant evidence related to mHealth interventions implemented at routine Peruvian HIV services.

Conclusion

In this study, a one-way SMS intervention tailored to a young adult PLWH population from a resource-constrained setting showed no strong effects across multiple HIV-care outcomes. Despite being crucial for HIV control, the overall retention in care rates observed here are far from the 90-90-90 treatment target envisioned by UNAIDS for 2020. To leverage on facilitating mHealth implementation within the health policy realm, future local interventions may benefit from additional SMS features, such as a two-way delivery platform, customization of contents and an automized delivery process articulated to the strategic participation of human health resources. Future research should thoroughly consider the variability in delivery of the intervention.

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References

1. Amico K, Mugavero M, Krousel-Wood M, Bosworth H, Merlin J. Advantages to Using Social-Behavioral Models of Medication Adherence in Research and Practice. Journal of General Internal Medicine. 2017;33(2):207-215.

2. Saag K, Bhatia S, Mugavero M, Singh J. Taking an Interdisciplinary Approach to Understanding and Improving Medication Adherence. Journal of General Internal Medicine. 2017;33(2):136-138.

3. Stricker S, Fox K, Baggaley R, Negussie E, de Pee S, Grede N et al. Retention in Care and Adherence to ART are Critical Elements of HIV Care Interventions. AIDS and Behavior. 2013;18(S5):465-475.

4. Mukumbang F, Van Belle S, Marchal B, van Wyk B. Exploring 'generative mechanisms' of the antiretroviral adherence club intervention using the realist approach: a scoping review of research-based antiretroviral treatment adherence theories. BMC Public Health. 2017;17(1).

5. Mukumbang F, Mwale J, van Wyk B. Conceptualising the Factors Affecting Retention in Care of Patients on Antiretroviral Treatment in Kabwe District, Zambia, Using the Ecological Framework. AIDS Research and Treatment. 2017;2017:1-11.

6. Horvath T, Azman H, Kennedy G, Rutherford G. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database of Systematic Reviews. 2012;.

7. Haberer J, Sabin L, Amico K, Orrell C, Galárraga O, Tsai A et al. Improving antiretroviral therapy adherence in resource-limited settings at scale: a discussion of interventions and recommendations. Journal of the International AIDS Society. 2017;20(1):21371.

8. Kanters S, Park J, Chan K, Socias M, Ford N, Forrest J et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. The Lancet HIV. 2017;4(1):e31-e40.

9. Ware N, Pisarski E, Tam M, Wyatt M, Atukunda E, Musiimenta A et al. The Meanings in the messages. AIDS. 2016;30(8):1287-1293.

10. Sabin L, Mansfield L, DeSilva M, Vian T, Li Z, Wubin X et al. Why it Worked: Participants' Insights into an mHealth Antiretroviral Therapy Adherence Intervention in China. The Open AIDS Journal. 2018;12(1):20-37.

11. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychology. 2008;27(3):379-387.

12. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W et al. The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. Annals of Behavioral Medicine. 2013;46(1):81-95.

13. Wood C, Hardeman W, Johnston M, Francis J, Abraham C, Michie S. Reporting behaviour change interventions: do the behaviour change technique taxonomy v1, and training in its use, improve the quality of intervention descriptions?. Implementation Science. 2015;11(1).

14. Muench F, Van Stolk-Cooke K, Morgenstern J, Kuerbis AN, Markle K. Understanding messaging preferences to inform development of mobile goal-directed behavioral interventions. J Med Internet Res. 2014 Feb;16(2).

15. Sillice MA, Dunsiger S, Jennings E, Lantini R, Bock BC. Differences in mobile phone affinity between demographic groups: implications for mobile phone delivered interventions and programs. mHealth. 2018;4:39.

16. Finitsis D, Pellowski J, Johnson B. Text Message Intervention Designs to Promote Adherence to Antiretroviral Therapy (ART): A Meta-Analysis of Randomized Controlled Trials. PLoS ONE. 2014;9(2):e88166.

17. De Leon E, Fuentes L, Cohen J. Characterizing Periodic Messaging Interventions Across Health Behaviors and Media: Systematic Review. Journal of Medical Internet Research. 2014;16(3):e93.

18. Gibson D, Tamrat T, Mehl G. The State of Digital Interventions for Demand Generation in Low- and Middle-Income Countries: Considerations, Emerging Approaches, and Research Gaps. Global Health: Science and Practice. 2018;6(Supplement 1):S49-S60.

19. Cash-Gibson L, Felix L, Minorikawa N, Pappas Y, Gunn L, Majeed A et al. Automated telephone communication systems for preventive healthcare and management of long-term conditions. Cochrane Database of Systematic Reviews. 2012.

20. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging telemedicine for facilitating self management of long-term illnesses. Cochrane Database of Systematic Reviews. 2008.

21. Aranda-Jan C, Mohutsiwa-Dibe N, Loukanova S. Systematic review on what works, what does not work and why of implementation of mobile health (mHealth) projects in Africa. BMC Public Health. 2014;14(1).

22. Marcolino M, Oliveira J, D'Agostino M, Ribeiro A, Alkmim M, Novillo-Ortiz D. The Impact of mHealth Interventions: Systematic Review of Systematic Reviews. JMIR mHealth and uHealth. 2018;6(1):e23.

23. Gritz E, Danysh H, Fletcher F, Tami-Maury I, Fingeret M, King R et al. Long-term Outcomes of a Cell Phone–Delivered Intervention for Smokers Living With HIV/AIDS. Clinical Infectious Diseases. 2013;57(4):608-615.

24. Devi B, Syed-Abdul S, Kumar A, Iqbal U, Nguyen P, Li Y et al. mHealth: An updated systematic review with a focus on HIV/AIDS and tuberculosis long term management using mobile phones. Computer Methods and Programs in Biomedicine. 2015;122(2):257-265.

25. Reddy A, Huseman T, Canamucio A, Marcus S, Asch D, Volpp K et al. Patient and Partner Feedback Reports to Improve Statin Medication Adherence: A Randomized Control Trial. Journal of General Internal Medicine. 2016;32(3):256-261.

26. Marcum Z, Gellad W. Improving Medication Adherence: Keep Your Eyes on the Prize. Journal of General Internal Medicine. 2016;32(3):236-237.

27. Bayona E, Menacho L, Segura E, Mburu G, Roman F, Tristan C et al. The Experiences of Newly Diagnosed Men Who Have Sex with Men Entering the HIV Care Cascade in Lima, Peru, 2015–2016: A Qualitative Analysis of Counselor–Participant Text Message Exchanges. Cyberpsychology, Behavior, and Social Networking. 2017;20(6):389-396.

28. Menacho L, Blas M, Alva I, Roberto Orellana E. Short Text Messages to Motivate HIV Testing Among Men Who have Sex with Men: A Qualitative Study in Lima, Peru. The Open AIDS Journal. 2013;7(1):1-6.

29. Curioso WH, Quistberg DA, Cabello R, et al. “It’s time for your life”: How should we remind patients to take medicines using short text messages? AMIA . Annu Symp proceedings AMIA Symp. 2009;2009:129-133.

30. Ruiz EF, Proaño Á, Ponce OJ, Curioso WH. [Mobile health for public health in Peru: lessons learned]. Rev Peru Med Exp Salud Publica. 32(2):364-372. http://www.ncbi.nlm.nih.gov/pubmed/26338384. Accessed February 20, 2019.

31. Krishnan A, Ferro E, Weikum D, Vagenas P, Lama J, Sanchez J et al. Communication technology use and mHealth acceptance among HIV-infected men who have sex with men in Peru: implications for HIV prevention and treatment. AIDS Care. 2014;27(3):273-282.

32. Gardner L, Giordano T, Marks G, Wilson T, Craw J, Drainoni M et al. Enhanced Personal Contact With HIV Patients Improves Retention in Primary Care: A Randomized Trial in 6 US HIV Clinics. Clinical Infectious Diseases. 2014;59(5):725-734.

33. Prochazka M, Batey DS, Zinski A, Dionne-Odom J, Otero L, Rodriguez M, Gonzalez-Lagos E. “Improving appointment adherence among young adults with HIV in Peru with an mHealth intervention: a feasibility study”. IDSA 2017, in San Diego, USA, 4-8 October 2017. Accepted for poster presentation.

34. Dirección General de Intervenciones Estratégicas en Salud Pública, Dirección de Prevención y Control de VIH-SIDA, Enfermedades de Transmisión Sexual y Hepatitis. Technical Standard of health of integral attention of the adult with infection by the Human Immunodeficiency Virus (HIV). Ministerio de Salud. Lima; Perú. 2018 [cited 2020 Apr 10]. Available from: http://bvs.minsa.gob.pe/local/MINSA/4479.pdf

35. Tang Z, Pan SW, Ruan Y, Liu X, Su J, Zhu Q, et al. Effects of high CD4 cell counts on death and attrition among HIV patients receiving antiretroviral treatment: an observational cohort study. Nature Scientific Reports. 2017 Jun 9;7(1).

36. HIV/AIDS Bureau. HIV/AIDS Bureau Performance Measures [Internet]. Health Resources and Services

Administration. 2019 [cited 2020 Apr 10]. Available from: http://hab.hrsa.gov/deliverhivaidscare/coremeasures.pdf

37. Joseph Davey D, Nhavoto J, Augusto O, Ponce W, Traca D, Nguimfack A et al. SMSaúde: Evaluating mobile phone text reminders to improve retention in HIV care for patients on antiretroviral therapy in Mozambique. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2016;73(2):e23-e30.

38. Hoces Burga DA. Comparación de tres medidas de retención en el cuidado en pacientes adultos infectados con VIH que inician terapia antiretroviral en el Hospital Nacional Cayetano Heredia. Univ Peru Cayetano Hered. 2014.

39. Edelman EJ, Tate JP, Fiellin DA, Brown ST, Bryant K, Gandhi N, et al. Impact of defined clinical population and missing data on temporal trends in HIV viral load estimation within a health care system. HIV Med. 2015 Jul 1;16(6):346–54.

40. International ethical guidelines for health-related research involving humans. Geneva: the Council for International Organizations of Medical Sciences (CIOMS), 2017.

41. Pence BW, Bengtson AM, Boswell S, Christopoulos KA, Crane HM, Geng E, et al. Who Will Show? Predicting Missed Visits Among Patients in Routine HIV Primary Care in the United States. AIDS Behav. 2019 Feb 15;23(2):418–26.

42. Israelski D, Gore-Felton C, Power R, Wood MJ, Koopman C. Sociodemographic characteristics associated with medical appointment adherence among HIV-seropositive patients seeking treatment in a county outpatient facility. Prev Med (Baltim). 2001;33(5):470–5.

43. Ruiz Pizarro P. Ruiz Pizarro. Presentation presented at; 2018; Reunión Técnica de Hospitales, Institutos de GERESAS/DIRESAS/DIRIS del Norte del país.

44. Lester R, Ritvo P, Mills E, Kariri A, Karanja S, Chung M et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. The Lancet. 2010;376(9755):1838-1845.

45. Pop-Eleches C, Thirumurthy H, Habyarimana J, Zivin J, Goldstein M, de Walque D et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS. 2011;25(6):825-834.

46. Cooper V, Clatworthy J, Whetham J, Consortium E. mHealth Interventions To Support Self-Management In HIV: A Systematic Review. The Open AIDS Journal. 2017;11(1):119-132.

47. Quintana Y, Gonzalez Martorell E, Fahy D, Safran C. A Systematic Review on Promoting Adherence to Antiretroviral Therapy in HIV-infected Patients Using Mobile Phone Technology. Applied Clinical Informatics. 2018;09(02):450-466.

48. Amankwaa I, Boateng D, Quansah D, Akuoko C, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: A systematic review and meta-analysis. PLOS ONE. 2018;13(9):e0204091.

49. Linde D, Korsholm M, Katanga J, Rasch V, Lundh A, Andersen M. One-way SMS and healthcare outcomes in Africa: Systematic review of randomised trials with meta-analysis. PLOS ONE. 2019;14(6):e0217485.

50. Wald D, Butt S, Bestwick J. One-way Versus Two-way Text Messaging on Improving Medication Adherence: Meta-analysis of Randomized Trials. The American Journal of Medicine. 2015;128(10):1139.e1-1139.e5.

51. Ingersoll K, Dillingham R, Hettema J, Conaway M, Freeman J, Reynolds G et al. Pilot RCT of bidirectional text messaging for ART adherence among nonurban substance users with HIV. Health Psychology. 2015;34(Suppl):1305-1315.

52. Georgette N, Siedner M, Petty C, Zanoni B, Carpenter S, Haberer J. Impact of a clinical program using weekly Short Message Service (SMS) on antiretroviral therapy adherence support in South Africa: a retrospective cohort study. BMC Medical Informatics and Decision Making. 2017;17(1).

53. Lizárraga IRAC, Alvirio LAM, Pérez-Lu JE, Cavagnaro CC. Text messaging to improve patient adherence in haart: Randomized controlled trial. Rev Peru Med Exp Salud Publica. 2019;36(3):400–7.

54. Mayer J, Fontelo P. Meta-analysis on the effect of text message reminders for HIV-related compliance. AIDS Care. 2016;29(4):409-417.

55. Odeny T, Bukusi E, Cohen C, Yuhas K, Camlin C, McClelland R. Texting improves testing. AIDS. 2014;28(15):2307-2312.

56. Bigna J, Noubiap J, Kouanfack C, Plottel C, Koulla-Shiro S. Effect of mobile phone reminders on follow-up medical care of children exposed to or infected with HIV in Cameroon (MORE CARE): a multicentre, single-blind, factorial, randomised controlled trial. The Lancet Infectious Diseases. 2014;14(7):600-608.

57. Junod Perron N, Dominicé Dao M, Kossovsky M, Miserez V, Chuard C, Calmy A et al. Reduction of missed appointments at an urban primary care clinic: a randomised controlled study. BMC Family Practice. 2010;11(1).

58. Kliner M, Knight A, Mamvura C, Wright J, Walley J. Using no-cost mobile phone reminders to improve attendance for HIV test results: a pilot study in rural Swaziland. Infectious Diseases of Poverty. 2013;2(1).

59. Farmer T, Brook G, McSorley J, Murphy S, Mohamed A. Using short message service text reminders to reduce 'did not attend' rates in sexual health and HIV appointment clinics. International Journal of STD & AIDS. 2013;25(4):289-293.

60. Norton B, Person A, Castillo C, Pastrana C, Subramanian M, Stout J. Barriers to Using Text Message Appointment Reminders in an HIV Clinic. Telemedicine and e-Health. 2014;20(1):86-89.

61. Linnemayr S, Huang H, Luoto J, Kambugu A, Thirumurthy H, Haberer J et al. Text Messaging for Improving Antiretroviral Therapy Adherence: No Effects After 1 Year in a Randomized Controlled Trial Among Adolescents and Young Adults. American Journal of Public Health. 2017;107(12):1944-1950.

62. Musiimenta A, Atukunda EC, Tumuhimbise W, Haberer JE. Resilience after withdrawing a technology-based medication adherence support intervention from people living with HIV in rural Uganda. AIDS Care - Psychol Socio-Medical Asp AIDS/HIV. 2018 Aug 23;30(sup5):S89–96.

Supporting Information

S1 Table. Comparison of primary and secondary outcomes by study groups

Outcomes	Study groups		Unadjusted effect size (95% CI) †	p value	Adjusted effect size (95% CI) †	p value
	SMS (n = 80)	Control (n = 320)				
	no. (%)					
Primary outcomes						
Retention in care	40 (61%)	195 (61%)	0.99 (0.80-1.23)	0.96	0.93 (0.75-1.16)	0.52
ART initiation[a]	55 (83%)	254 (79%)	1.21 (0.90-1.61)	0.21	1.08 (0.80-1.47)	0.62
ART pick-up visits*						
First semester	8 (6-9)	7 (3-8)	1.12 (0.98-1.28)	0.09	1.07 (0.94-1.22)	0.29
Second semester	6 (6-7)	6 (6-6)	0.99 (0.90-1.09)	0.85	0.99 (0.91-1.09)	0.91
Third semester	6 (5-6)	6 (5-6)	0.99 (0.91-1.08)	0.90	0.99 (0.91-1.08)	0.84
Secondary outcomes						
Viral suppression at 1st year[o]	30 (45%)	151 (47%)	1.06 (0.78-1.43)	0.72	0.99 (0.74-1.35)	0.99
Viral suppression at 1st year[#]	30 (73%)	151 (81%)	0.90 (0.73-1.10)	0.31	0.92 (0.75-1.13)	0.45
Loss to follow-up[a]	31 (47%)	144 (45%)	1.01 (0.69-1.49)	0.95	1.16 (0.76-1.79)	0.49

†Effect sizes were assessed as risk ratios (SMS group/Control group). Adjusted analyses on all outcomes included the following baseline covariates: education level, pregnancy and available CD4 count.
* Median (interquartile range) are displayed.
[a] Hazard ratios are calculated.
[o]This regression assumed missing viral loads as being virally non-suppressed.
[#] This regression used only subjects with available viral load values.
Of note, linearity assumption was not met for CD4 numerical variable in the adjusted model.