

Use of the telephone for accessing people living with HIV/AIDS to antiretroviral therapy: systematic review

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Abstract *This paper aims to evaluate the effectiveness of telephone use for the adherence of people with HIV/AIDS to antiretroviral therapy. A systematic review was carried out in the following databases: Latin American and Caribbean Literature in Health Sciences (Lilacs/ Bireme), SCOPUS, Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), Web of Science; and in the Scientific Electronic Library Online (SciELO) and Cochrane libraries, using the following descriptors: “HIV”, “Cell Phones”, “Acquired Immunodeficiency Syndrome” and “Antiretroviral Therapy, Highly Active”. We gathered a sample of 17 papers. The proposed cellphone interventions were the use of cellular applications, Short Message Service, and telephone calls. In most studies, telephone use has had a significant impact on adherence to treatment. The evaluation of the studies showed good methodological quality and adequate allocation secrecy. Self-reported adherence emerged among the adherence measuring methods. Cellphone use was effective in improving adherence to antiretroviral therapy for people living with HIV.*

Key words HIV, Acquired Immunodeficiency Syndrome, Cell phones

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Introduction

The advancement of antiretroviral therapy (ART) reduced the morbidity and mortality associated with infection and consequently increased the life expectancy of people living with HIV/AIDS (PLWHA)¹. The effectiveness of ART can only be achieved through good adherence to drugs², in order to prevent viral resistance, the appearance of opportunistic diseases, increased virus transmission, higher probability of developing to the final stage of the disease and the reduced survival³.

It is a challenge to reach and maintain ideal levels of adherence to ART due to individual, social, and systemic barriers that hamper this process⁴. Studies indicate that despite the availability of ART drugs, some difficulties concerning adherence to therapy and prevalence rates of non-adherence ranging from 51.3%^{1,5} to 25%⁶ are observed.

An interest in the use of Information and Communication Technologies (ICTs) has occurred in recent years, and ICTs have had a significant impact on the quality of services and people's lifestyles. Their implementation in the health sector is emerging as one of the areas with the highest growth rates today. Among the primary technologies are electronic devices such as the telephone, which has gained popularity and stands out as a strong ally in the treatment of chronic diseases⁷.

In the context of HIV/AIDS, studies have shown the advantages of using the telephone to improve care services for this population, with impacts on improving quality of life, social support, self-care^{8,9} and adherence to ART^{8,10-12}.

Thus, the development of efficient methods to improve adherence of people with HIV/AIDS to ART is required. In this context, telephone use can be an available resource to promote adherence to PLWHA treatment since it is inexpensive and easily accessible among patients and health professionals. Therefore, this study aimed to evaluate the effectiveness of telephone use for the adherence of people with HIV/AIDS to antiretroviral therapy.

Methods

A systematic review was carried out, a secondary study type that allows the investigation of relevant research on a particular theme in order to undertake a critical and comprehensive review of

the literature, providing the incorporation of new trends in clinical practice and the consequent evidence-based refreshing of professionals¹³.

The systematic review followed the seven steps recommended by Cochrane collaboration¹⁴: formulation of the research question; study sites; critical evaluation of research; data collection; analysis and presentation of information.

The research question was outlined from the PICO strategy, which is an acronym for Patient (adults living with HIV), Intervention (Use of the telephone), Comparison (standard care) and Outcomes (treatment adherence)⁸. Thus, the following guiding question was established: "How effective is telephone use to promote PLWHA adherence to ART?"

We included clinical trials that investigated interventions with telephone use aimed at promoting adherence of PLWHA to ART regardless of language and year of publication. The exclusion criteria defined were: literature reviews, letters, opinion papers, experience reports, case studies, book chapters, congress presentations, repeated publications, studies with children and papers that did not respond to the research question.

The electronic search was performed by two reviewers simultaneously in October 2017, in three databases – Latin American and Caribbean Literature in Health Sciences (LILACS/BIREME), SCOPUS and Web of Science; portal Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed) and the Scientific Electronic Library Online (SciELO) and Cochrane libraries.

The search strategy employed the following descriptors in Portuguese, English, and Spanish: "HIV", "Cell Phones", "Acquired Immunodeficiency Syndrome" and "Antiretroviral Therapy, Highly Active", combined with the Boolean operator AND in Portuguese, English, and Spanish. Descriptors were selected using the Health Sciences Descriptors (DeCS) and the Medical Subject Heading (MeSH). Cross-linkings were: [HIV and Cell Phones]; [Acquired Immunodeficiency Syndrome and Cell Phones]; [Antiretroviral Therapy, Highly Active and Cell Phones]; [HIV and Cell Phones and Antiretroviral Therapy, Highly Active]; [Acquired Immunodeficiency Syndrome and Cell Phones and Antiretroviral Therapy, Highly Active].

A total of 758 papers were found from cross-linkings, and 17 were selected. Of these, 29 were duplicated, and 712 did not answer the guiding question because they addressed the following

topics: acceptance of the proposed interventions, perceptions of the individuals about the interventions, reflections on advances in the use of technologies to improve adherence. The final sample consisted of 17 papers, six from SCOPUS, five from MEDLINE/PubMed, three from Web of Science and three from Cochrane. Figure 1 shows the identification, selection, and inclusion of research papers.

The criteria for evaluating the quality of the studies were carried out by applying the Jadad's Quality Scale¹⁵, whose scores range from 0 to 5, with low-quality studies scoring below three. The analysis was performed from the following questions: 1a. Was the study described as random? (use of words such as “randomized”, “random”,

“randomization”); 1b. Was the method adequate? 2a. Was the study described as double-blind? 2b. Was the method adequate? 3. Was there a description of the losses and exclusions?

Papers were also analyzed and classified concerning allocation secrecy into Category A – allocation secrecy adequately carried out and described; Category B – the study was described as random, but the randomization method or of the allocation secrecy are not described; Category C – the allocation secrecy was inappropriate; and Category D – the study was not random¹⁴.

Data were analyzed by two independent authors, translating and reading the papers in full. The information was transcribed and organized from a validated instrument¹⁶, which investigated authorship, year, the country where the study was conducted, objective, methodological development, proposed technology, results, and conclusion. Therefore, we opted for a detailed review of the information found.

Regarding ethical issues, paper integrity and copyright were respected, and there was no change in the content found for the benefit of this research.

Results

All studies consisted of clinical trials and covered a total of 2,720 adults with HIV using ART, published from 2010 to 2017. Most studies were conducted in the U.S.^{7,17-22}, as well as African countries, such as Kenya⁸⁻⁹, Uganda²³, South Africa²⁴ and Nigeria¹⁰, Asian countries²⁵⁻²⁸, and Brazil²⁹ (Chart 1). The interventions proposed were use of cellphone applications^{20,23}, Short Message Service (SMS)^{7-10,17,21,22,24-29} and telephone calls^{18,19,26,28} (Chart 1).

The use of the application consisted of a program installed in the cellphone with several features such as a clock with the 24-hour drug, showing the schedule of the daily dose of the participant's therapy, which recorded the days and times of drug intake; graphical representations of the estimated plasma concentrations of each ART drug; and a simulation of immune activity comprising a representation of the CD4 + T lymphocyte count and viral load, based on the most recent blood tests. This application allowed the participants' real-time visualization of the physiological effects of their adherence to ART^{19,29}.

The SMS consisted of text messages sent from cellphones. The content of the message was motivating and worked as a reminder to take the ART

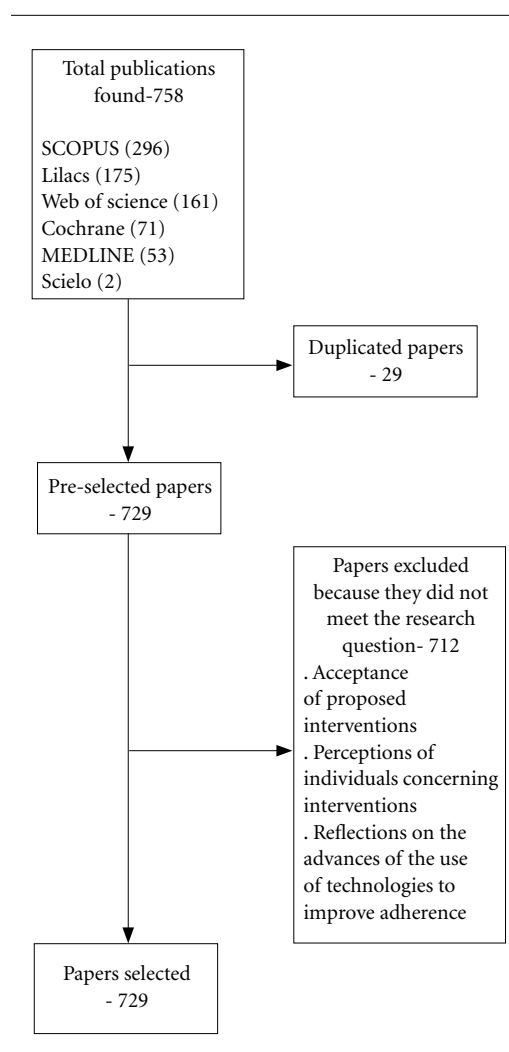


Figure 1. Flowchart of the identification, selection, and inclusion of the studies. Fortaleza (CE), Brazil, 2017.

Chart 1. Characterization of the studies. Fortaleza (CE), Brazil, 2017.

| Authors, year, country | Intervention employed | Sample | Follow-up time | Results |
|--|-----------------------|---|----------------|---|
| Hardy et al. (2011), EUA ⁷ | *SMS | 23 **IG: 10/ ***CG: 9 | 6 weeks | The mean adherence was 79% through self-report and 65% by counting tablets at the onset of the study in both groups. Over 6 weeks, adherence increased in the IG concerning: tablet count [**** M:76.3% ± **** SD: 20.5], self-report [M: 83.1% ± SD: 26.2], ***** DEM [M: 73.9% ± SD: 27.3] and composite adherence score [M: 70.6% ± SD: 24.8] |
| Lester et al. (2010), Quênia ⁸ | SMS | 538 IG: 273/CG: 265 | 48 weeks | Adherence was reported by 168 of the 273 patients of the IG compared to 132 of the 265 of the CG (***** RR for non-adherence = 0.81; ***** [95% CI=0.69-0.94; ***** p=0.006) |
| Pop-Eleches et al. (2011), Quênia ⁹ | SMS | 431 IG: 302/CG:139 | 48 weeks | 90% IG adherence compared to 40% CG adherence (p=0.03) |
| Maduka; Tobin-West (2013), Nigéria ¹⁰ | SMS | 104 IG: 52/CG:52 | 16 weeks | 76.9% of the patients in the IG adhered to the drug treatment as opposed to 55.8% in the CG (p=0.022). The IG CD4 + lymphocyte count increased to 578.0 cells/ml compared to 361.5 cells/ml recorded in the CG (p=0.007) |
| Dowshen et al. (2012), EUA ¹⁷ | SMS | 25 IG e CG: information not available | 24 weeks | Self-reported adherence increased in the IG compared to baseline (74.7) in weeks 12 (93.3) (p<0.001) and 24 (93.1) (p<0.001) |
| Kalichman et al. (2011), EUA ¹⁸ | Telephone calls | 40 IG: 21/CG: 19 | 16 weeks | Adherence was improved in the IG from 87% of the tablets taken at the onset of the intervention to 94% at the end of the intervention (p<0.01) |
| Belzer et al. (2014), EUA ¹⁹ | Telephone calls | 37 IG: 19/CG: 18 | 24 weeks | Self-reported adherence was higher in IG compared to CG (p=0.007) |
| Swendeman et al. (2015), EUA ²⁰ | Cellphone application | 50 IG: 34/CG: 16 | 6 weeks | The correlations were relatively high in the IG and CG by including 100% adherence of the participants (***** r=0.70-0.73) |
| Rana et al. (2016), EUA ²¹ | SMS | 32 enrolled 20 concluded IG and CG: information not available | 24 weeks | 18 of the 32 participants had a viral load < 20 copies/ml at the onset of the study, and 25 (78%) participants had viral suppression (< 20 copies/ml, p=0.002) |
| Garofalo et al. (2016), Chicago ²² | SMS | 109 IG: 55/CG: 54 | 48 weeks | The mean adherence between the IG was higher than in the CG (95% CI: 0.91-13.9), and the odds ratio for ≥ 90% adherence was 2.57 (95% CI: 1.01-6.54). Adherence increased from 28% at baseline to 64% at 3 months and slightly decreased to 61% at 6 months' follow-up in the IG, whereas the CG achieved 24% at baseline and 43% and 51% at baseline at 3 and 6 months' follow-up, respectively. |
| Perera et al. (2014), Uganda ²³ | Cellphone application | 28 IG: 17/CG: 11 | 12 weeks | IG showed better adherence (p=0.03) when compared to CG |

it continues

Chart 1. Characterization of the studies. Fortaleza (CE), Brazil, 2017.

| Authors, year, country | Intervention employed | Sample | Follow-up time | Results |
|--|-------------------------|------------------------|----------------|--|
| Orrrell et al. (2015), África ²⁴ | SMS | 230 IG: 115/CG: 115 | 48 weeks | Adherence was 82.1% in the IG compared to 80.4% in the CG [OR: 1.08; 95% CI: 0.77-1.52] |
| Sabin et al. (2015), China ²⁵ | SMS | 119 IG: 63/CG: 56 | 24 weeks | Adherence was similar in the two groups, with improved adherence by 52 of the 63 of the IG (82.5%) compared to 29 of the 56 of the CG (51.8%) (RR 1.59; 95% CI: 1.21-2.10 p<0.001) |
| Shet et al. (2014), India ²⁶ | Telephone calls and SMS | 631 IG: 315/CG: 316 | 96 weeks | Adherence was similar between IG and CG (RR [CI=95%] = 0.93-1.65, p= 0.14) |
| Swendeman et al. (2015), Índia ²⁷ | SMS | 90 IG: 46/CG: 44 | 4 weeks | In the IG, missed doses of medications were reduced from 39% to 18%, and ratios of missed doses fell from 44% to 17% |
| Abdulrahman et al. (2017), Malásia ²⁸ | SMS and Telephone calls | 224 IG: 116/CG: 108 | 24 weeks | Adherence was higher in the IG (95.7; 95% CI: 94.39-96.97) than in the CG (87.5; 95% CI: 86.14-88.81). An increased CD4 + lymphocyte count (p = 0.017) was found in the IG, and the viral load was higher (p=0.001) in the CG |
| Costa et al., (2012), Brasil ²⁹ | SMS | 21 IG: 8/CG: 13 | 20 weeks | The adherence of the participants in the IG was higher than in the CG (tablet counts [50.0% in the IG and 38.4% in CG], self-report [100.0% in the IG and 84.6% in CG], DEM [75.0% in the IG and 46.1% in the CG], but no statistically significant difference was found between the results |

*SMS: Short Message Service **IG: Intervention Group; ***CG: Control Group; ****M: mean; *****SD: Standard Deviation; *****DEM: Drug Event Monitoring; *****RR: Relative Risk; *****CI: Confidence Interval; *****p: p-value; *****r: correlation coefficient; *****odds ratio.

drugs and influenced behaviors to improve adherence²⁹. In one study, participants should confirm receipt of the message; otherwise, a beep would be sent every 15 minutes to the patient⁷.

The intervention based on telephone calls was directed to the users' portable devices and aimed to investigate the medication intake and possible missed doses in the last days, as well as provide advice to promote adherence¹⁸.

Follow-up time ranged from 4 (one month) to 96 (24 months) weeks. Improved adherence was identified in fourteen studies^{7-10,17,21-24,27-29}, and interventions were ineffective in three of them^{20,25,26}.

Concerning the frequency of intervention, daily frequency prevailed^{7,17,19-25,27}. Three studies used frequency on alternate days^{8,10,29}, two were weekly^{26,28}, one fortnightly¹⁸, and another study compared the use of daily and weekly intervention⁹. As for the professionals who applied the intervention, the study team with unspecified professional category was highlighted (82.3%)^{7,9,10,17,18,20,22-25,27,29}, followed by researchers who were not involved in the routine of the patients (5.8%)²⁶, as well as the mention of higher education health categories, such as nurses (11.8%)^{8,28} and doctors (5.8%)²⁸ (Chart 1).

Regarding methods for measuring ART adherence, self-reported adherence^{7,8,10,17-20,22,23,26-29}, the drug monitoring system (MEMS)^{7,9,21,25,29} the tablet count^{7,18,29}, the composite adherence score⁷, the pharmacy records^{19,25}, the CD4+ T lymphocyte count^{10,28} and the evaluation of the viral load^{19,22-24,28} were highlighted. Some studies were submitted to a combination of different forms of measuring adherence^{7,10,17-19,22,23,28,29} (Chart 1).

In self-reported adherence, patients reported the prescribed medication, drugs ingested, and the number of doses missed in the last days²⁹. Other papers analyzed adherence through the use of instruments such as Medication Adherence Report Scale (MARS), which consists of specific questions about the dose ingested and doses missed in the last 28 days, organized on a Likert scale²³; and the Visual Analogue Scale (VAS), which analyzes the rate of adherence in the last 4 weeks on a scale from 0% to 100%, correlating with the tablet count recalled in the last three days and the viral load¹⁷.

MEMS was also a strategy used to measure adherence and consists of a wireless device placed in the medication container that records the date and time of each opening of the vial for antiretroviral ingestion, communicating immediately through a radio service to a central server²⁵.

Other studies measured adherence by counting tablets, delivering the medication at an initial meeting, and counting tablets at the end of a given period²⁸. The composite adherence score (CAS) was also adopted, which is a method based on both the tablet count and MEMS⁷.

Pharmacy replenishment records were an additional method of assessing adherence, providing information on the number of tablets released to patients, and calculation of prescribed tablets, taking into account the number of tablets dispensed²³. The CD4+ T lymphocytes^{10,28} and viral load were also measured by laboratory tests^{19,23}.

Chart 2 shows the characterization of the studies by author, year and country of publication, sample, intervention used, follow-up time, results concerning the improvement of adherence, the Jadad's scale score and allocation secrecy.

The evaluation of the quality of the studies shows good methodological quality, with a predominance of scores higher than 3^{9,10,18-20,22,24-26,28,29}. Regarding the allocation secrecy, there was an emphasis on Category A – adequate allocation secrecy process, except for four studies whose allocation secrecy was not described^{17,9,19,20} and two that were not random^{17,27} (Chart 2).

Discussion

The use of ICTs in the context of HIV increases access to health services and promotes communication between the professional and the patient on a real-time basis, providing self-care and disease management. The efficacy of these technologies on adherence to ART is associated with providing social support, patient self-assessment about therapeutic follow-up, knowledge about HIV, and management of side effects – conditions that help the patient to establish a daily routine and to solve problems related to taking tablets³⁰.

Real-time ICT professional follow-up promotes information and education for adherence, allowing patients to report side effects and quickly adjust their behavior to improve adherence. Also, the use of technologies as a reminder to take ART drugs as per medical prescription improves the drug dose self-management behavior²⁵.

Technology-mediated health care is seen as a ubiquitous glance and permanent attention of professionals concerning the daily life of PLWHA, motivating adherence to treatment behavior, and promoting emotional support to fight against

Table 2. Study quality evaluation. Fortaleza (CE), Brazil, 2017

| Authors, year | Jadad's Scale* | Allocation secrecy** |
|---|----------------|----------------------|
| Hardy et al. (2011) ⁷ | 3 | B |
| Lester et al. (2010) ⁸ | 3 | A |
| Pop-Eleches et al. (2011) ⁹ | 4 | B |
| Maduka; Tobin-West (2013) ¹⁰ | 4 | A |
| Dowshen et al. (2012) ¹⁷ | 1 | D |
| Kalichman et al. (2011) ¹⁸ | 5 | A |
| Belzer et al. (2014) ¹⁹ | 4 | B |
| Swendeman et al. (2015) ²⁰ | 4 | B |
| Rana et al. (2016) ²¹ | 3 | A |
| Garofalo et al. (2016) ²² | 5 | A |
| Perera et al. (2014) ²³ | 3 | A |
| Orrell et al. (2015) ²⁴ | 5 | A |
| Sabin et al. (2015) ²⁵ | 5 | A |
| Shet et al. (2014) ²⁶ | 4 | A |
| Swendeman et al. (2015) ²⁷ | 1 | D |
| Abdulrahman et al. (2017) ²⁸ | 5 | A |
| Costa et al., (2012) ²⁹ | 5 | A |

Note: * Classification that evaluates the quality of the study and the score ranges from 0 to 5, and studies of low quality are those with scores lower than 3. ** The allocation secrecy classification is as follows: Category A – allocation secrecy adequately performed and described; Category B – the study was described as random, but there is no description of the randomization type nor of the allocation secrecy; Category C – the allocation secrecy was inappropriate; and Category D – the study was not random.

diagnosis-related depressive feelings³¹. Thus, frequent communication between professional and patient works as direct counseling, promoting time, and financial costs savings^{31,32}.

As evidenced in this review, the use of technologies to extend health care to PLWHA brings beneficial impacts in the short and long term, promotes viral suppression, prevents disease progression, and reduces drug resistance and morbidity. It is emphasized that an intervention time of at least six months is recommended²⁸ in order to achieve positive results on biological markers.

Despite the advantages associated with the use of technologies to promote adherence to ART, some difficulties may compromise cell phone use in health care, such as the lack of credits, handling difficulty, keeping the battery charged, network problems, loss of access, change of number, restricted time of telephone use, breach of confidentiality and concern with the disclosure of the serological status to third parties^{7,32,33}.

Given the above, it is necessary to develop intervention strategies that are inexpensive, effective, and that seek to involve the patient with the health service³⁴. Also, it is essential to know the patients' perceptions and needs vis-à-vis these technologies, identifying the barriers and solving the problems to seek the development of effective technologies¹⁹. It is, therefore, necessary to compare technologies and seek the most appropriate ones for each context.

Regarding the frequency of intervention, the weekly messages were more widely accepted and caused more significant impact and better adherence to ART when compared to daily reminders. This can be explained by the frequent and repeated stimulation that causes discomfort in the patients and may invade their privacy⁹.

Regarding the adherence measurement methods, self-reported adherence, which is less expensive and more comfortable to analyze, but subjective and error-prone and may result in overestimated values³⁵ prevailed. Thus, one must associate these self-reported measures with clinical markers such as viral load, CD4+ lymphocytes, and other more objective means of assessing adherence, such as tablet count, MEMS and pharmacy records^{7,23,29,36}.

Regarding the quality of the clinical trials analyzed, four reached the maximum score in Jadad's Scale¹⁵, indicating that a significant number of the studies were double-blind. It was evidenced that double-blind produces more consistent results by reducing selection biases and ensuring the reliability of the information collected¹⁵.

Conclusion

The use of the telephone as a tool to support the care of adults with HIV/AIDS was effective in improving adherence to ART and the relationship between professionals and patients. The phone was used in different ways and involved the use of applications on the device with internet access, text messaging, and telephone calls. Text messages stood out for their low cost. The limitations associated with using the telephone were accessibility and training for the use of electronic devices.

Future experimental studies with telephone use should consider the comparison of intervention methods, the association of methods of measurement and comparison between objective methods, factorial clinical trials (multiple interventions) and comparison between the frequency of applied interventions. Also, one should consider and develop more research that seeks to identify user perception of the most efficient interventions.

The limitation of the review was the impossibility of carrying out meta-analysis from the selected studies due to the heterogeneity of the clinical trials concerning the different measures of adherence to ART, the different variable endpoint and the lack of statistical data, which impaired the calculation of the summary measures.

Collaborations

VF Santos, AKB Costa, ICV Lima and HO Alexandre: Conception and design, collection, analysis, interpretation of data and active participation in the discussion of results. Writing of the article or relevant critical review of the intellectual content. Compliance with all aspects of the manuscript in terms of the accuracy or completeness of the information. MTG Galvão and E Gir: Review and final approval of the version to be published. Compliance with all aspects of the manuscript in terms of the accuracy or completeness of the information. VF Santos and AKB Costa: Review and final approval of the version to be published.

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