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Interventions to Promote Adherence to Antiretroviral Therapy of People Living with HIV/AIDS

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ABSTRACT

The aim of the study was to evaluate the effectiveness of interventions to promote adherence to antiretroviral therapy of people living with HIV/AIDS. We conducted a systematic review of the literature in the databases LILACS, SciELO, MEDLINE, CINAHL, Scopus and Cochrane, between May and July 2016. We used the keywords "Medication Adherence" and "Antiretroviral Therapy, Highly Active" combined with the Boolean operator AND. It wasfound1589 articles and 26 were selected to analysis. Interventions found include: short message service, telephone call, individual and collective monitoring, directly observed therapy and single tablet regimen. Also, it was found that, in general, the reported results showed that interventions were effective in promoting the adherenceto antiretroviral therapy of people living with HIV/AIDS. It is concluded that the use of targeted interventions for PLWHA in order to increase adherence to ART are effective strategies that improve the health status of patients.

Keywords: Medication adherence; HIV; Acquired Immunodeficiency Syndrome

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INTRODUCTION

With the development of antiretroviral therapy (ART), AIDS has become a chronic disease [1]. The treatment seeks to raise the CD4 T lymphocyte levels and maintain viral suppression while preserving immune function and preventing progression to the most advanced stage of the disease [2]. Furthermore, it improves the quality of life, reduces the cost of health care and extendstheglobal survival [3]. However, to maintain healthand get good clinical results, it is critical that people living with HIV/AIDS (PLWHA) have adequate treatment adherence [4]. Adherence to therapy is a dynamic process that involves physical, mental, social, cultural, behavioral, demographic and economic aspects [5]. Side effects, complex treatment regimens, stigma, lack of social support, low educational level, difficulty to move up to the drug distribution units and mood disorders are factors associated with poor adherence to ART [2,6]. However, some factorsinfluence on the improvementof adherence to treatment, such as the desire to live, religious practices, concern abouttheir health and the desire to be healthy to take care of their children [2]. Pharmacological monitoring of PLHIV on antiretroviral treatment is a strategy to identify problems related to the medication, which enables the implementation of targeted interventions that will promote the safety and therapeutic efficacy [7]. Aprospective study noted that 35.4% of PLWHA stopped taking the medication at least once during the one year of follow up [8], this implies the need for efforts to improve adherence by developing interventions and support strategies [9]. Given the above and in order to move forward in improving the health conditions of the population living with HIV/AIDS, this study aims to evaluate the effectiveness of interventions to promote adherence to antiretroviral therapy of people living with HIV/AIDS.

EXPERIMENTAL SECTION

We conducted a systematic review, which provides a summary of the evidence related to any specific intervention, by applying methods and critical analysis, facilitating the planning of clinical research in health [10].
The research question was designed based on the PICO strategy, which is an acronym for Patient (Adults living with HIV), Intervention (Use of initiatives/ strategies), Comparison (Standard care) and Outcomes (Treatment adherence) [11]. Thus,it was established the following guiding question: "What is the effectiveness of interventions to promote adherence to antiretroviral therapy of people living with HIV/AIDS?"
It was included clinical trials that investigated interventions directed to promote adherence to ART of PLWHA, regardless of language and the year of publication. Exclusion criteria were: repeated publications, studies with children and articles that did not answer the research question.
The electronic search was carried out by two reviewers simultaneously from May to July 2016, in four data bases: Cumulative Index toNursingandAllied Health Literature (CINAHL), Latin American and Caribbean Health Sciences (LILACS/BIREME), Scientific Electronic Library Online (SciELO) and SCOPUS; a portal: Medical LiteratureAnalysisandRetrievalSystem Online (MEDLINE/PubMed) and the Cochrane Library.
For search strategy, we used the following descriptors: "MedicationAdherence" and "AntiretroviralTherapy, Highly Active" combined with the Boolean operator AND. The descriptors were selected through the Health Sciences Descriptors (DeCS) and Medical SubjectHeading (MESH).
In the study selection stage, a careful analysis of the title and summary of the 1589 identified publications was conducted; being 1516 articles excluded because they did not met the research question orthey were repeated. The 73 remainingpublications were read in full, after this, 47articles were excluded for not answering the research question(they analyzed interventions with children, patient experiences, description of interventions, adhesion barriers to ART and validation of questionnaires for monitoring adherence). Therefore, the final sample consisted of 26 studies. Figure 1 shows the identification, selection and inclusion of the research articles.

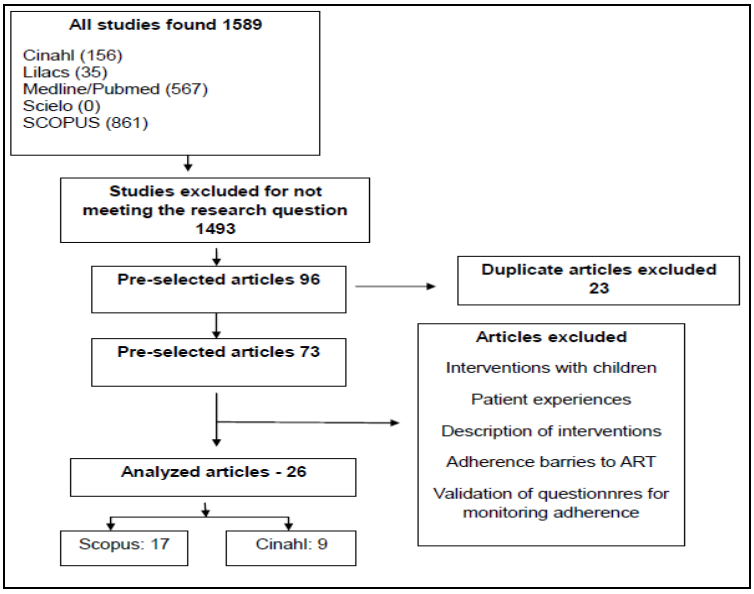

Figure 1: Flowchart of studies' identification, selection and inclusion

Data analysis was performed using translation and readingof the full articles by two authors independently. In case of doubt, there was a meeting between the reviewers to reach an agreement. For the analysis it was used a predefined instrument with the following information: author, year, country where the study was conducted, aim, proposed technology, number of participants, methods and results. The findings were discussed with basis of scientific literature on the theme, and respecting the integrity of the articles and copyrights, with no modification of the content found in favor of this research.

RESULTS AND DISCUSSION

All studies were clinical trials and covered a total of 4032 adults with HIV in use of HAART. As for the place of realization, most studies have been developed in the United States of America (USA) [12-16], as well as in other African countries, Mozambique [17] and Cameroon [18].

The proposed interventions were Short Message Service (SMS) [18,19], phone call [13, 20-22], use of letters [16], psychoeducational activities [23,24], Directly Observed Therapy (DOT) [25,26], Directly Observed Therapy - Motivational (DOT-m) [17], single pill regimen [27], life-windows [28], life-step [12], graphics [14], resolution theory problems [29], behavioral motivation [30], treatment assistant [26], treatment schedules [26], individual counseling [13, 19,22, 31-34], group counseling[16] and ecosystem counseling[35]. The follow-up of the subjects ranged from 4 (one month) to 96 weeks (24 months).

The SMS was composed of text messages using mobile phones. The message content was motivating and served as a reminder to take medication. In addition, the message used the "delivery report" to ensure that the messages were delivered to the participants [18, 19]. The intervention telephone call consisted of telephone calls directed to mobile devices of the users.The patients received,frequently, calls from the researchers without notice, to know about taking medication [13,20-22].The electronic alarm was a battery-powered device that worked as an electronic reminder to remind the patient to take the medication [21].

In the intervention with use of cards, one card with a printed image and a color for each of antiretroviral drugs were developed, besides the dosing schedule and side effects. Then, the material was placed in envelopes and mailed to patients with motivational messages and medications taken reminders [16]. The psychoeducational activities were composed of in-person meetings with the participants and the aim was to encourage behavioral changes to medication intake [23, 24].

In the DOT, daily, patients went to the medication withdrawal station to ingest supervised dose of the therapy, at that time the nightly and weekends doses were delivered [25, 26]. On the other hand, in DOT-m, besides the patient withdraw the dose of supervised medication, he had the support of a person accompanied him and provided information related to the medication, such as benefits and side effects, and a set of strategies aiming to develop skills to incorporate the taking of medication in their daily lives [17].

The single pill regimen was an intervention to fit antiretroviral therapy in a single tablet containing the drugs of choice for professionals (in the case zidovudine, lamivudine and abacavir) with fixed-dose, reducing the number of ingested pills [27].

The Life-windows was a program consisting of several sequential components that accompanied the participants by software, which had overall assessment modules, directed to adhesion-promoting intervention activities with audio interactive activities [28].The Life-step was an electronic web intervention that consisted of a single-session program that included video and a test that lasted between 33-90 minutes,which followed a few steps seeking to provide information on antiretroviral therapy and adherence, following one cognitive-behavioral approach to identify potential barriers to adherence and propose the accession improvement strategies such as creating a daily schedule of medication, development of reminder strategies and encouraging social support [12].

The image-guided intervention was based on pictorial information particularly relevant for medication regimen, through the use of graphic images. This intervention focused on providing information for treatment adherence, including the importance of following the instructions required for each drug. It was also included motivational techniques as providing direct feedback on the participant's health status and self-monitoring of changes in adherence and viral load [14].

The problem-solving theory consisted of a five-step process, which dealt with: to identify the barriers of participants for adherence to therapy, seeking possible solutions, select the best option, monitor its implementation and to observe the participant's adherence[29]. In behavioral motivation, therapists used the motivational intervention and counseling to explore the thoughts, feelings, motivations and behaviors related to participants' adherence to therapy. It was usedstrategies that included providing personalized feedback with goal setting and change planning as well as solving problem plans[30].

Treatment assistant was an intervention model in which patients took one person that he trusts for consultations, this person is called treatment assistant and he/she worksto incentive and assist in the medication adherence process. Another technique used was the timing of treatment, this was an intervention that besides the basic advice on ART, patients receivedscheduled education messages about medication and adherence [26].

Individual counseling were interventions with trained professionals that addressed situations of health care such as guidance on adherence to antiretroviral, administration of medication, the patients' beliefs about therapy, reasons for missed doses and use of alcohol and other drugs [13, 19, 31-35]. The group intervention occurred through group

sessions using motivational interviewing, seeking to empower patients to make decisions and develop strategies about taking ART [15, 21, 35, 35].

In ecosystem counseling, patients and their social support network, whether family, partners, relatives, friends or professionals attended counseling conducted by trained professionals, seeking to improve the social support and increase adherence to therapy [37]. Another intervention that sought to promote adherence to treatment strengthening social support was the model of peer support intervention, which consisted of group meetings, where all patients enrolled in medication receive location participated and made a "pair" with another patient, being called "meetings in pairs". In addition, it was also encouraged to carry out phone calls between pairs [36].

Promoting adherence was identified in seventeen studies [12, 14, 17, 19, 20, 22-26, 27-30, 32, 34, 35], in one study the adherence worsened [37] and in eight, the interventions were not effective [13, 15, 16, 18, 21, 31, 33, 36]. On ways of implementing the intervention, there was a predominance of combination with standard care represented by: patient education[24, 28, 30], use of technologies [12, 13, 14, 18, 19, 20-22), counseling sessions for use of ART [13, 14, 16, 19, 22, 29, 31, 33, 34] and individual or group counseling [17, 23, 25-27, 30, 37].

Regarding to the frequency of offering the intervention, predominated the weekly frequency [14, 18, 20, 21, 23, 29, 30, 32, 36, 37, 35], followed by monthly[13, 19, 25, 28, 29]. Four studies used daily frequency [13, 17, 27, 32] and two biweekly [21, 31]. The studies which developed weekly interventions showed significant improvement in adherence to drug therapy [14, 20, 28, 29, 30, 32, 35].

As for the professionals who applied the intervention, there was mention of different categories, such as nurses [15, 26, 31, 32, 34, 35], pharmacist [12, 22, 24], physicians [24, 31, 33] and technical professionals from other areas [17-21, 24, 26, 29, 30, 36, 37].In other studies it was not possible to identify who applied the intervention [13, 14, 23, 25, 27, 28]. About methods of measuring adherence to ART, the highlights were the self-reported adherence [12, 17, 21, 22, 26, 32-34, 36, 37], pill count [12, 14, 25, 32], monitoring system of medical events [13, 15, 19, 21, 22, 29, 31-35], Pharmacy records on supply [14] and use of questionnaires [27, 28].There have been studies in which the combination of different forms of measurement of adhesion was carried out [12, 18, 22, 32, 33, 34].

Self-reported adherence on patients informs the medication prescribed,the amount of drugs ingested and the amount of missed doses in the last days [12, 16, 17, 22, 23, 26, 32, 33]. Other articles analyzed self-adhesion by applying an instrument called AIDS Clinical Trials Group (ACTG) [21, 36],or its adapted version [34, 37].Other studies measure the adherence by pill count, where a monthly phone call without notice was performed and the patient reported the amount of pills ingested [12, 14, 20, 23, 25, 32] or by using an instrument to define the percentage of ingested and prescribeddrugs, namedThe Time Line Follow-Back (TLFB) [30].

It was also used other questionnaires to measure adherence, such as the Simplified Medication Adherence Questionnaire (SMAQ), which is a self-report questionnaire containing six items whose questions address patients'health and missed doses in the last days [24, 27] as well astheVisual Analogue Scale [18, 28].

The Medication Event Monitoring System (MEMS) was also a strategy used to measure adherence. It was used a device that recorded the opening of the bottle of pills, each time the pot was opened, it was considered that the patient had ingested the medication [13, 15, 19, 21, 22, 29, 31-35]. Some studies have indicated the pharmacy records of refueling as a way to assess adherence. In this case, the pharmacy gave information about the number of tablets released to patients and from this it was done the calculation in relation to prescription pills, taking into account the number of released pills [14, 18].

For better visualization of the analyzed studies, it was decided to present a brief description of the 26 articles considering its authors, type of intervention, frequency of intervention, howthe adherence was measuredand effectivenessof the intervention. It was found that, in general, the reported results showed that interventions were effective in promoting the adherence to antiretroviral therapy of people living with HIV/AIDS. (Table 1).

Adherence to ART is important to get better results in the treatment and health of PLHIV, since low adherencetotherapy may result in worsening of the patients'clinical condition, resulting in an increased viral replication, disease progression and drug resistance [6].This may indicate the need for therapeutic regimes increasingly complex that generally requires a greater number of pills,thiscan be considered a threat to both the individual and the public health system[5].

It was observed that the phone (call or SMS) is an important technology used to promote adherence to treatment. The World Health Organization (2008) [38] recognizes that communication technologies can promote a health care focused on the needs of each patient. Also, it allows increased access to services and specialists, shaping up as an important complementary health care tool in countries with uneven distribution of health professionals.

Table 1: Articles analyzed according to type of intervention, frequency of intervention, how the adherence was measured and effectiveness of the intervention

Author	Type of intervention	Intervention frequency	Adherence measurement	Effectiveness
PEARSON *et al*., 2007	DOT-m	Daily	Self-report	Effective
SORENSEN *et al*., 2007	Individual counseling	Daily	Two or more methods	Effective
LANGEBEEK *et al*., 2014	Single pill regimen	Daily	Questionnaire	Effective
KOENIG *et al*., 2008	Group counseling	Weekly	Monitoring system	Effective
BLANK *et al*., 2011	Group counseling	Weekly	Two or more methods	Effective
INGERSOLL *et al*., 2011	Individual/Group counseling	Weekly	Questionnaire	Effective
GROSS *et al*., 2013	Counseling / Phone calls	Weekly	Monitoring system	Effective
HIMELHOCH *et al*., 2013	Phone calls	Weekly	Pills count	Effective
KALICHMAN *et al*., 2013	Counseling	Weekly	Two or more methods	Effective
SIMONI *et al*., 2011	Individual counseling / Alarm	Weekly	Two or more methods	Effective
MUGUSI *et al*., 2009	DOT	Monthly	Self-report	Effective
BERG *et al*., 2011	DOT	Monthly	Pills count	Effective
FISHER *et al*., 2011	Software	Monthly	Questionnaire	Effective
SABIN *et al*., 2015	SMS	Monthly	Monitoring system	Effective
RATHBUN *et al*., 2005	Individual counseling	Not mentioned	Two or more methods	Effective
RUIZ *et al*., 2010	Group counseling	Not mentioned	Questionnaire	Effective
CLABORN *et al*., 2014	Software	Not mentioned	Two or more methods	Effective
PELLOWSKI *et al*., 2014	Phone calls	Daily	Monitoring system	Not effective
WEBEL, 2010	Group counseling	Weekly	Questionnaire	Not effective
MBUAGBAW *et al*., 2011	SMS	Weekly	Two or more methods	Not effective
REZNICK *et al*., 2013	Group counseling	Weekly	Self-report	Not effective
SIMONI *et al*., 2007	Group counseling	Biweekly	Two or more methods	Not effective
BASSO *et al*., 2013	Individual counseling	Biweekly	Monitoring system	Not effective
LEVIN *et al*., 2006	Letters	Not mentioned	Questionnaire	Not effective
WILSON *et al*., 2010	Individual counseling	Not mentioned	Two or more methods	Not effective
HOLSTAD *et al*., 2012	Group counseling	Not mentioned	Monitoring system	Not effective

A study showed that PLWHA proved to be satisfied when they received phone calls as a means of health intervention [39]. On the other hand, patients who received phone messages express concern regarding disclosure of HIV status [40]. The use of general language, not using specific terms for HIV, may be one of the measures adopted by the professionals who apply to intervention in order to minimize the risk of disclosing the diagnosis.

Other strategies used to increase adherence to treatment were: the promotion of social support, group therapy and peer support. It is known that the family and social support is a key to fighting the disease, with positive repercussions on the accession process [41].

Routine monitoring of adherence to ART is a recommended strategy for the care of PLWHA, especially in places with few resources available, where there is no availability of second and third line drug treatment [42]. It was found a variety of ways to measure the adherence to ART, this may be due to the difficulty inevaluatethe adherence, requiring multiple combination approaches, as seen in the studies, including qualitative measures [6].

It was observed that the self-reported adherence was the measurement most commonly used to assess the adherence. This type of measurement has the advantage of being less expensive and easier to be analyzed, but it is subjective and is prone to errors and may result in overestimation of values [6]. Thus, it is necessary to associate these self-reported measures with clinical markers such as viral load, CD4 T lymphocytes and more objective means of assessing adherence [9].The pills count was another form of adherence assessment. This method when measured by professionals can be considered a precise technique, however, it can be masked by the patient when the pill is discarded and not consumed [6].

It was noted that the MEMS has been used both to describe the adherence as compared to adherence measurement techniques in environments with limited resources. However, this method also has its limitations and challenges, such as the difficulty to train patients on how to use the bottles of drugs with the electronic device. One of the most reliable ways to make this measurement would be to use ElectronicDrugs Monitors (EDM) associated with the serological results, but these methods are not recommended for routine monitoring due to the high cost, making its use restricted in resource-limited settings [42].

Most of the interventions found were directed only to improve adherence to drug treatment.However it is essential the developmentof interventions that address adherence and mental health of PLHI, since depression is associated with lower adherence to ART, regardless of adherence measure used [43]. Moreover, it is still necessary to develop intervention strategies that are low cost, effective and that involve the patient in the health service, since patients

who have support from health professionals, have high levels of adherence to treatment [44]. Therefore, it is important that health professionals recognize the difficulties faced by PLWHA, so they can map out effective strategies [8].

CONCLUSION

The use of targeted interventions for PLWHA in order to improve adherence to antiretroviral therapy was effective, improving the health condition of patients. Although, it was identified some interventions that were ineffective and only one that worsened the adherence status of the patient, most of the interventions promoted adherence to pharmacological treatment. Most of the interventions were applied by higher education professionals and often they used technological resources, such as alarm devices, computer programs and mobile phones. The use of mobile phones it is highlighted because it allows the contact in real time between professionals and patient.The patient follow-up was longer than four weeks. As regards the frequency of offering the interventions, it was observed that the weekly interventions showed significant improvement in adherence to drug therapy.

There was also a variety of techniques to measure the adherence to ART, including, self-report, pill counts, pharmacy records of refueling, the use of questionnaires and the Medication Event Monitoring System. It is noteworthy that in relation to this latter form of measurement there were challenges and difficulties on the part of patients to properly handle the equipment. This study highlights the effectiveness of interventions to promote adherence to ART by PLWHA as a way to improve the health care of this population, which makes this subject relevant and instigates new research. Further, it is emphasizes the importance of professionals in the assistance to PLWHA, aiming at a comprehensive care and a better quality of life of this population.

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