REVISTA DA ESCOLA DE ENFERMAGEM DA USP
JOURNAL OF SCHOOL OF NURSING · UNIVERSITY OF SÃO PAULO

REVIEW

doi: https://doi.org/10.1590/S1980-220X2019009803627

Effectiveness of interventions for adherence to antiretroviral therapy in adults with HIV: a systematic review*

Efetividade de intervenções para adesão à terapia antirretroviral em adultos com HIV: revisão sistemática

Eficacia de las intervenciones para la adhesión al tratamiento antirretroviral en adultos con VIH: revisión sistemática

How to cite this article:
Zuge SS, Paula CC, Padoin SMM. Effectiveness of interventions for adherence to antiretroviral therapy in adults with HIV: a systematic review. Rev Esc Enferm USP. 2020;54e03627. doi: https://doi.org/10.1590/S1980-220X2019009803627

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* Extracted from the thesis: "Intervenções para a promoção da adesão a terapia antirretroviral de adultos com a infecção pelo HIV: revisão sistemática da literatura", Programa de Pós-Graduação em Enfermagem, Universidade Federal de Santa Maria, 2018.

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ABSTRACT

Objective: To identify the best available evidence of intervention effectiveness for adherence to antiretroviral therapy for HIV in adults. **Method:** The methodology proposed by the Cochrane Collaboration was used, with search in the databases: PubMed, Embase, LILACS, CINAHL, Web of Science and SCOPUS. Randomized clinical trials of interventions to promote adherence to antiretroviral therapy for HIV, in the ≥ 18-year-old population, published from 2010 onward, were considered. The eligibility, inclusion and extraction of results were developed by two independent researchers. **Results:** The five studies included in the quantitative analysis were effective interventions that developed educational actions with the patient, especially mediated by software, the use of medication schedule reminders and the inclusion of treatment supporters that also received educational actions to develop such role. **Conclusion:** The combination of interventions strengthens the promotion of adherence. There is a need for investment in the implementation of educational actions with patients, such as the inclusion of supporters, in addition to counseling and electronic devices for reminders, which must be offered in the services in an articulated and continuous manner.

DESCRIPTORS

Acquired Immunodeficiency Syndrome; HIV; Antiretroviral Therapy, Highly Active; Medication Adherence; Systematic Review.

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Received: 04/15/2019
Approved: 11/07/2019

INTRODUCTION

The United Nations Program on the Human Immunodeficiency Virus (HIV) and the Acquired Immune Deficiency Syndrome (AIDS), UNAIDS, declared the goal to end the epidemic by 2030. The program recognizes that this will lead to increased efforts, global solidarity, evidence-based actions and multisectoral partnerships. The goal is for, by 2020, 90% of all people with HIV to know that they have this virus, 90% of all people with diagnosed HIV infection to receive antiretroviral therapy (ART) without interruption and 90% of all people receiving ART to have viral suppression. Therefore, this goal is called 90-90-90[1].

In order to achieve viral suppression, it is necessary that the person maintains adherence to the therapy[2]. The World Health Organization (WHO) defines adherence as the person's degree of behavior in line with the recommendations of health professionals. Such behavior refers to taking the medication, following a diet and making changes in their lives. Moreover, WHO also clarifies that adherence involves five dimensions: socioeconomic factors, factors related to the patient, factors related to the disease, factors related to the treatment, and the healthcare system and team[3].

The document, among other studies, shows that there are methods for monitoring adherence, however there is no gold standard for such assessment[3-5]. The evaluation is indicated based on the monitoring of medication intake, however, in the literature, there is a diversity of cutoff points for reference in the classification of the measure and assessment of adherence, for example, from 80 to 100% of doses. Other assessments are made by missed doses or schedules, failure to follow dietary prescriptions or medication dispensing records. Another necessary distinction is the establishment of the assessment period (monthly, weekly or daily), with longer periods for assessments related to the registration of medication dispensation, and shorter periods for self-report of adherence[6-9].

There are also validated scales to assess adherence to therapy, which classify the result as: adherence and non-adherence; or categorize it into high, medium and low adherence; or strict, adequate and inadequate adherence[10]. Despite the different nomenclatures, the results have pointed to the need for investment in promoting adherence, since the difficulties of maintaining it are evident[11-13].

Regarding the difficulties, researchers invest in intervention studies to assess adherence and its effectiveness. However, they still point to the need to keep monitoring the implementation of interventions in clinical practice, considering its support in scientific evidence[14-17]. Thus, one developed this systematic review, which aimed to identify the best available evidence of intervention effectiveness for adherence to antiretroviral therapy for HIV in adults.

METHOD

Type of study

This is a systematic review of the literature, which followed the methodology established by the Cochrane Collaboration[18].

Selection criteria

The selection criteria were: primary studies that presented interventions to promote adherence to ART in adults infected with HIV, ≥ 18 years old, randomized clinical trial (RCT) that had as one of the outcomes the assessment of adherence, which could be based on self-report, pill count or electronic monitoring, and published from 2010 onward[19].

The research question was: what is the effectiveness of interventions to promote adherence to antiretroviral therapy for HIV infection in the adult population?

Data collection

The search for primary studies occurred in February 2017, in the following electronic databases: Publisher Medline (PubMed), Excerpta Medical Database (Embase), Latin American Literature in Health Sciences (LILACS), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science (WoS) and Elsevier SciVerse Scopus (SCOPUS). The search strategy was composed based on the descriptors [vírus da imunodeficiência humana OR síndrome da imunodeficiência adquirida] AND [terapia antirretroviral de alta atividade OR adesão à medicação] AND [ensaio clínico randomizado], with combinations adjusted to each database.

A total of 6,674 records were identified. The screening, eligibility and inclusion were developed in a double independent way and the disagreements were submitted to the evaluation of a third reviewer. The initial relevance test was developed after the exclusion of repeated records by reading the title and abstract of 5,340 articles, when it was verified whether the primary study met the topic, the timeline and the object of intervention. The relevance test I was developed with the full reading of 56 articles, when it was verified whether they were in accordance with the type of study, the population, the outcome and the type of intervention, and 43 articles were excluded[18].

Data analysis

Thirteen articles were submitted to methodological quality assessment, which was developed through seven questions with scores on a scale of 0 to 5 points. The higher the score, the better the methodological quality. Thus, an RCT that reached five points was classified as rigorous, whereas the one below three points was considered of low quality[20]. Four articles scored less than three points and were excluded from this systematic review. Nine articles were analyzed considering the result of the effectiveness of the intervention in adherence, when the results were compared in the

control and experimental groups. A total of four articles were excluded, in which the interventions were not effective for adherence. The sample consisted of five articles, and the selection process is presented in a flowchart (Figure 1).

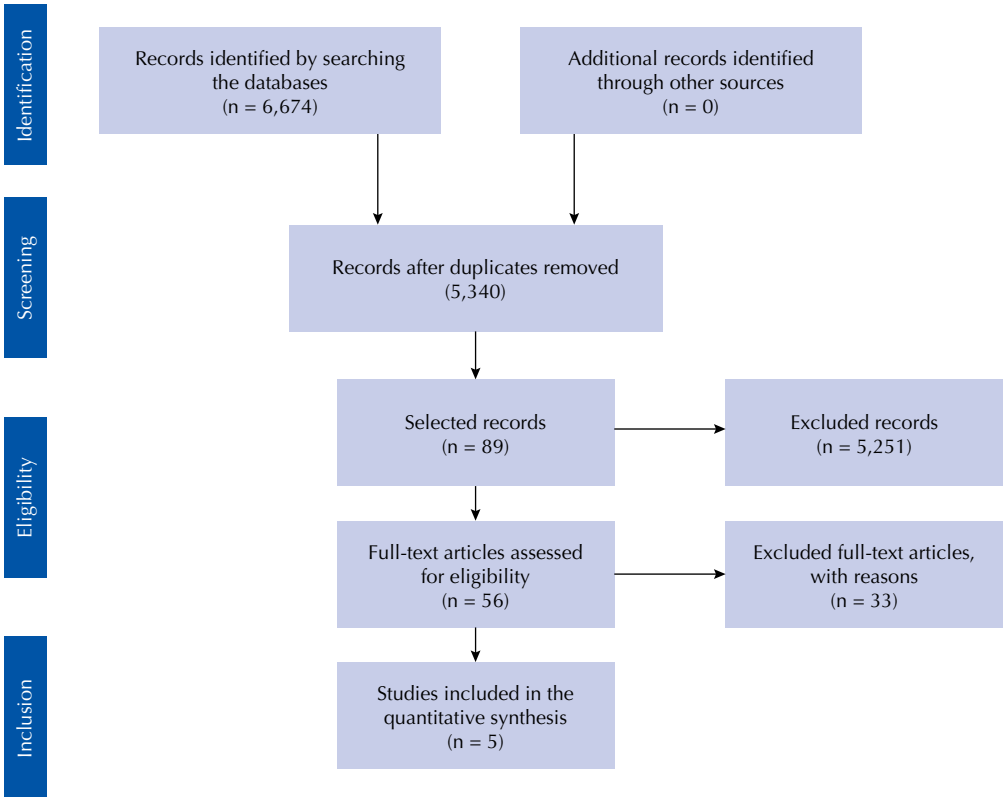

Figure 1 – Flow of the process of identification, screening, eligibility and inclusion of studies in the systematic review – Santa Maria, RS, Brazil, 2017.

The five articles included were submitted to the risk of bias assessment, through the following criteria: selection bias, performance bias, detection bias, attrition bias and reporting bias. The risk of bias assessment in each domain was defined as "low risk of bias", "high risk of bias" or "unclear risk of bias"[18].

The data extraction included: study objective, inclusion criteria, number of participants, randomization, length of follow-up, age and gender of participants, primary and secondary outcomes, adherence evaluation, intervention groups, analysis of studies, results of interventions and conclusions. The synthesis was presented in a descriptive manner, with detailed information from each primary study.

RESULTS

The primary studies varied in length of follow-up of the RCT and presented different interventions[21-25] (Chart 1).

Chart 1 – Identification of studies included in the review, objective, sample, length of the control follow-up, type of intervention by group – Santa Maria, RS, Brazil, 2017.

Study	Objective	Sample / Follow-up	Control Group / Experimental Group / Intervention
Fisher, et al; (2011)[21]	To evaluate the efficacy of Life Windows as an intervention to support adherence to antiretroviral therapy based on computer monitoring.	CG - 176 EG - 152 LF - 18 months	CG – Standard-of-care EG – Life Windows I - Interactive program-based software with 20 educational and attitudes modules.
Kunutsor, et al; (2011)[22]	To assess the effectiveness of the treatment support initiative as an intervention in improving clinical attendance for antiretroviral drug refills and adherence to antiretroviral therapy	CG - 83 EG - 83 LF - 7 months	CG - Standard adherence intervention package EG - Treatment supporter intervention I - Family members received educational material on support actions with the patient.

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Study	Objective	Sample / Follow-up	Control Group / Experimental Group / Intervention
Simoni, et al; (2011)[23]	To evaluate an adherence improvement intervention through counseling and electronic reminders among HIV-positive patients.	CG - 34 EG - 36 LF - 3 months	CG – Standard intervention EG - Standard intervention, alarm device, counseling. I - Electronic alarm device (reminder), counseling (individual or with adherence partner/in-person or telephone) or both.
Kalichman, et al; (2011)[24]	To test the effects of a theory-based integrated behavioral intervention for reducing HIV transmission risks and improve treatment adherence.	CG - 210 EG - 192 LF - 10 months	CG – Support group EG - Integrated behavioral intervention I - Behavioral intervention based on conflict theory of decision making.
Gross, et al; (2013)[25]	To determine whether an intervention derived from problem solving theory (Managed Problem Solving) would improve antiretroviral outcomes.	CG - 66 EG - 58 LF - 9 to 12 months	CG – Usual care EG – Managed Problem Solving I - Five steps to identify barriers, potential solutions, the best option, monitoring and usefulness.

CG – Control Group; EG – Experimental Group; I – Intervention; LF = Length of Follow-up.

Regarding the assessment of adherence, it was found that the primary studies used the pill count[21-22,24] as an assessment method, including through electronic devices[23,25].

Regarding the risk of bias assessment, its distribution was classified mostly with low risk of bias (Figure 2).

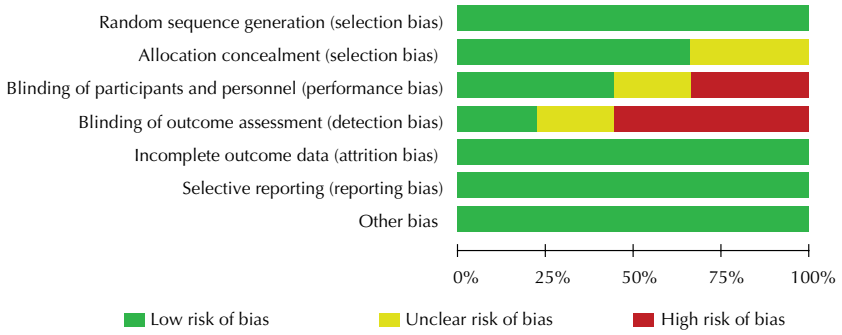

Figure 2 – Risk of bias assessment of the studies in the systematic review – Santa Maria, RS, Brazil, 2017.

Regarding the blindness assessment of the outcome evaluators domain, a high risk of bias was identified in three studies[21-23,24] (Figure 3).

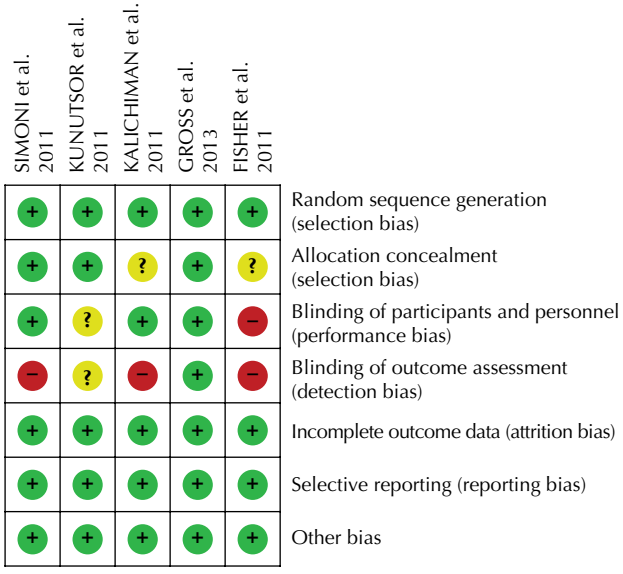

Figure 3 – Risk of bias assessment for individual studies by domains – Santa Maria, RS, Brazil, 2017.

Characteristics of interventions

Among the interventions that showed effectiveness for adherence to ART, LifeWindows[21] had the best result. The intervention consisted of a program (software) with 20 modules, in which introductory sessions were applied to both groups and intervention sessions (strategy selection, intervention activity and goal selection) only to the EG. The participants accessed the software (one control session or intervention per month) at regular appointments, for approximately 18 months. The chance of having perfect adherence was 12% higher compared with the standard assistance provided by the service over a period of three months. However, the results demonstrated that, in the short term, such assessment did not show a significant difference.

For the intervention to support ART[22], the CG received individual and group guidance about adherence, self-monitoring with the use of a logbook and tracking delays in the follow-up. Support from a family member was added to the EG, and the patient chose the relative, who then received educational material on actions to support adherence. Such intervention proved itself to be effective, with 4.5% more chances of having perfect adherence compared with standard adherence interventions.

Another intervention used an alarm device and/or counseling[23], and started with an appointment before the start of ART for both groups; an educational session about treatment plans, potential side effects and the importance of adherence; and with the offer of a schedule of daily medication, a daily dose organizer, a reference card for the support group and an electronic medication monitoring device. At the end of the baseline session, the participants were randomized into the CG (minimal intervention) and EG (intervention extended by 13 weeks with three additional telephone counseling sessions, inclusion of treatment partner in face-to-face session and electronic reminders). This intervention had a 5% higher possibility for perfect adherence when assessed through the self-report of adherence, and 2.2% higher when assessed through pill counting, considering the period of 19 weeks.

In the integrated behavioral intervention for risk reduction and adherence[24], both groups followed the same operational procedures with five group sessions and one individual counseling session. The CG received information on health improvement in general. The EG received specific information, based on the conflict theory of decision making, for treatment, adherence and safe sex. This intervention had a 4% higher possibility for patients to present improvement in adherence compared with those who participated in the support group.

In the problem-solving management intervention[25], the CG continued the follow-up in the health service. The EG received an educational session about the prescribed plan, expectations of medication adherence, side effects and misperceptions (for example, "if you drink alcohol, do not take medication"). Problem solving addressed daily routines, memory and cognitive assistance for taking pills, as well as social support as an incentive. Within two weeks, the group had the first monthly follow-up meeting, followed by three more. During the first three months, weekly telephone calls were made, and in the nine subsequent months the calls were made monthly. This intervention presented the lowest effectiveness, with a 2.3% higher possibility of having perfect adherence during the first year of follow-up compared with the people who perform the usual care.

DISCUSSION

In the studies included in this systematic review, the effective interventions to promote adherence to ART for HIV infection, in the adult population, have implemented educational actions with the patient[21,23-25], the use of medication reminder devices[23] and inclusion of treatment supporters who also received educational actions to develop such role[22-23].

Educational actions with the patient seek both the access to information for the management of therapy[21,23] and the resolution of conflicts/problems that can negatively interfere in adherence[24-25]. They were developed in sequential sessions and through different means, such as face to face, telephone, educational material and software.

Regarding educational actions with the patient, a longitudinal study conducted with 437 participants in Atlanta (Georgia, US) ascertained the relationship between medication adherence and other health behaviors, pointing out that the bivariate linear regression for communication about health was significant in the item "I have gathered information on things that affect my health"[26]. An intervention study carried out with HIV patients in a limited literacy South African population obtained results that support the importance of investing in educational actions. The intervention, which used an illustrated information leaflet, significantly increased knowledge (62.0-94.4%) and self-efficacy in patients over the six-month period, with improvement at each subsequent interview[27].

Regarding the intervention time, the long-term period had better effectiveness rates, which indicates the need for continuity of actions in health services, in order to maintain adherence rates. There is a concern with the assessment of both the time of application of the intervention and the time of maintenance of use.

According to the results of a systematic review of studies that specified the time invested in each counseling session, those that lasted between 30 and 60 minutes per session were effective, whereas those that lasted more than 1 hour or less than 10 minutes were not effective in adherence. Regarding the time between sessions, effectiveness was obtained when there was an interval of 06 months between sessions. Although some interventions present effectiveness in the first months, but not in the subsequent months, other interventions suggest that there are better results in a long-term process. It is not yet possible to determine the period that the intervention should last, due to the lack of consistency in the characteristics of the intervention and the methodology, including the costs of maintaining such assessment in the long term[28].

Regarding the type of intervention with the best effectiveness for adhering to the implementation of educational and interactive actions, softwares enabled uniformity in the set of information about the disease, motivations, skills and barriers that interfere in the behavior for adherence, and yet could embrace a greater number of patients. There is an investment in developing and assessing such technologies[29-30]. A computerized counseling intervention showed that ART adherence at the final follow-up was 13 points higher in the EG (p=0.038)[31]. It is worthy to note that computerized interventions have proven themselves to be effective in the scientific literature.

In a global research on adherence to HIV/AIDS-related medication from 1980 to 2017, it was found that the main documents focused on the impact of text messages on improving medication adherence[32]. In a data meta-analysis of 85 trials with 16,271 participants, short message service (SMS) interventions were superior to standard care in improving adherence with odds ratio [OR] 1.48 and 95% credible interval [CrI] 1.00-2.16[17]. In another meta-analysis, short message service (SMS) interventions had a statistically significant effect on adherence, with a risk difference = -0.10 and a 95%

confidence interval (CI) with result of -0.17 to -0.03[33]. Nationally, a methodological study validated the content of ten telephone messages to promote health in people with HIV (CVI = 0.98)[34].

The use of medication reminder devices was an effective adherence intervention[23]. Patients face difficulties in adhering to therapy, including forgetting. Thus, electronic devices that use audible and/or visual signals are available to remind or alert about taking the medication. The positive effects on adherence vary by the context of the reminders, the target group and the usability of the devices[35].

A cross-sectional quantitative study conducted in Ethiopia with 423 patients on ART identified a high proportion of patients with a cell phone, willing to use it as medication reminders (AOR = 2.22, 95%CI [1.09, 4.52]) [36]. Converging with this result, a study to assess patient interest in a smartphone mobile application (app) to assist in medication adherence, with a total of 101 patients surveyed in Columbus (Ohio, US), pointed out that 72.3% had a smartphone and 70.3% were interested in downloading and using an adherence app. Patients desired to receive appointment reminders (87%), notifications to schedule appointments (85%), refill notifications (83%), medication reminders (79%) and adherence tracked by pharmacy (59%) [37]. These results indicate perspectives on the potential use of technology to promote adherence.

A systematic review of nine RCTs showed that the phone was the type of information and communication technology with proven efficacy with respect to adherence. Integrated use (SMS, calls, alarm and Web) promotes increased access to care, strengthening the relationship between patients and health services, with the possibility of mitigating the difficulties in reaching optimal levels of adherence[38].

However, there is concern about maintaining the effects of the interventions. A qualitative study conducted in Uganda, with former participants of a pilot randomized controlled trial, observed that the benefits related to the intervention may persist, since most participants demonstrated resilience through learning the intervention, internalizing the habit of adherence and employing adaptive coping strategies, such as using alarms and adjusting medication time to their routine[39].

Interventions that included treatment supporters[22-23] were effective in adherence, since the support of a family member, friend or professional contributes to the improvement of the patient's mental health, providing well-being, better coping with the serological condition and improvement of their quality of life.

This efficacy converges with results such as those of the cross-sectional community-based study, which assessed the factors that contribute to ART drug adherence among adults living with HIV, conducted in a rural community in Machakos County, Kenya. The immediate family was rated high in providing social support (3.7±0.6), followed by social support groups (3.1± 0.8). Marital status (p = 0.019) contributed significantly to the prediction of ART adherence[40].

A longitudinal study that assessed the relationship between adherence and other health behaviors among adults with HIV found that the more an individual endorsed communicating to others about their health, the more likely they were to be adherent. Bivariate linear regression for communication about health was significant in the item "I have discussed my health with friends or family"[26].

An RCT meta-analysis of peer-based interventions to promote adherence to ART in HIV populations found that peer support in combination with other interventions offers modest improvement in adherence. These effects may be due to the fact that, in many settings, particularly in low and middle-income countries, programs include treatment supporters. Thus, rather than introducing new interventions, it is suggested to invest in improving the quality in the delivery of existing services[41].

From this systematic review of the literature, an effort can be seen in the development of RCT, in response to global efforts, to improve adherence to ART for HIV, in order to improve people's quality of life and decrease HIV infection rates. However, each of the assessed primary studies presented a different intervention. Due to the heterogeneity of the types of intervention, it was not possible to carry out a meta-analysis.

This review was limited to the outcome of the adherence behavior. One recommends that future primary studies on interventions for adherence include associations with other health outcomes, as well as the other dimensions that involve adherence. Thus, there would be a better approximation with the WHO indications[3]. Although one has used comprehensive search strategies, it is possible that some articles have not been retrieved.

CONCLUSION

One found strong evidence of the effectiveness of educational actions, reminders to promote adherence to ART and treatment supporters. The result has shown efforts in interventions in two dimensions of adherence, indicated by WHO, which are: social factors related to supporters and factors related to the patient. The positive evaluation of the evidence indicates the need to increasingly consider the possibility of programs and routines to improve the situation in the health system. Interventions with key populations seem to be necessary, since studies with this population were scarce, which indicates that future studies should meet these specificities.

However, there are gaps in knowledge production, indicating the need for studies that include the other dimensions of adherence, such as economic factors, with regard to the cost-effectiveness ratio, factors related to the disease, with other outcomes (biological markers - viral suppression, viral load or CD4), considering that these parameters are important in confirming improved adherence, and factors related to the treatment itself. These are the dimensions indicated as relevant, as well as the dimension of the

health system and team, especially when one considers that there is effectiveness in interventions that are maintained over the long term. Considering such multidimensionality, one understands that the combination of interventions strengthens the promotion of adherence.

The results also allow one to make considerations about the need for investment in greater methodological rigor in the area of the object of study of this review, and topics such as the cutoff points for reference in the classification and assessment of adherence are necessary.

RESUMO

Objetivo: Identificar a melhor evidência disponível de efetividade de intervenção para a adesão à terapia antirretroviral para o HIV em adultos. **Método:** Utilizou-se da metodologia proposta pela Cochrane Collaboration, com busca nas bases de dados PubMed, Embase, LILACS, CINAHL, Web of Science e SCOPUS. Foram considerados ensaios clínicos randomizados de intervenções de promoção da adesão à terapia antirretroviral para o HIV, na população ≥ 18 anos, publicados a partir de 2010. A elegibilidade, inclusão e extração de resultados foram desenvolvidas por dois investigadores independentes. **Resultados:** Os cinco estudos incluídos na análise quantitativa foram intervenções efetivas que desenvolveram ações educativas com o próprio paciente, especialmente mediada por software, o uso de lembretes de horário do medicamento e inclusão de apoiadores de tratamento que também receberam ações de educação para desenvolver tal papel. **Conclusão:** A combinação de intervenções potencializa a promoção da adesão. Há necessidade de investimento na implantação de ações educativas com os pacientes, como a inclusão de apoiadores, além do aconselhamento e de dispositivos eletrônicos para lembretes, que devem ser oferecidos nos serviços de modo articulado e continuado.

DESCRITORES

Síndrome de Imunodeficiência Adquirida; HIV; Terapia Antirretroviral de Alta Atividade; Adesão à Medicação; Revisão Sistemática.

RESUMEN

Objetivo: Identificar las pruebas disponibles sobre la eficacia de la intervención en el cumplimiento de la terapia antirretroviral para el VIH en adultos. **Método:** Se utilizó la metodología propuesta por Cochrane Collaboration, con búsqueda en las bases de datos PubMed, Embase, LILACS, CINAHL, Web of Science y SCOPUS. Se consideraron los ensayos clínicos aleatorios de intervenciones que promueven la adhesión a la terapia antirretroviral para el VIH en la población ≥ 18 años, publicados a partir de 2010. La elegibilidad, la inclusión y la extracción de los resultados las llevaron a cabo dos investigadores independientes. **Resultados:** Los cinco estudios incluidos en el análisis cuantitativo se referían a intervenciones eficaces que desarrollaron acciones educativas con el propio paciente y que fueron mediadas por programas informáticos, uso de recordatorios de horarios de medicación e inclusión de personal de apoyo al tratamiento que formó parte de acciones educativas para ejercer dicha función. **Conclusión:** La combinación de las intervenciones mejora la promoción de la adhesión. Es necesario invertir en la implantación de acciones educativas entre los pacientes, como la inclusión de personal de apoyo además de asesoramiento y de dispositivos electrónicos de recordatorio que deben ofrecerse en los servicios de salud articulada y continuamente.

DESCRIPTORES

Síndrome de Inmunodeficiencia Adquirida; VIH; Terapia Antirretroviral Altamente Activa; Cumplimiento de la Medicación; Revisión Sistemática.

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Financial support

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq). Process number 408709/2016-2.