DOI: 10.1590/1413-81232018247.22312017

Factors associated with antiretroviral therapy adherence in adults: an integrative review of literature

Patrícia Paiva Carvalho (http://orcid.org/0000-0002-7072-320X) [1]
Sabrina Martins Barroso (http://orcid.org/0000-0003-1759-9681) [2]
Heloisa Correa Coelho (https://orcid.org/0000-0002-6988-4874) [1]
Fernanda Rodrigues de Oliveira Penaforte (https://orcid.org/0000-0001-8483-1562) [3]

Abstract *AIDS is an advanced clinical manifestation of HIV infection. It generates severe immunodeficiency and associated infections that may lead to death. The antiretroviral therapy (ART) has reduced the morbimortality of HIV/AIDS, but its benefits depend on ART adherence. This integrative review followed the PICO method to identify factors associated with adult adherence to ART. Empirical papers published between January 2010 and December 2016 in the Medline, SciELO, Lilacs and PePSIC databases were included. We analyzed 125 papers regarding the characteristics of studies, adherence measures and associated factors. Results showed a wide variety in the definition of adherence and the use of measures for its monitoring, as well as several adherence-associated factors. These were categorized as follows: 1- Individual variables; 2- Treatment characteristics; 3- HIV/aids infection characteristics; 4- Relationship with the health services; 5- Social support. Health services should characterize the users' profiles, systematize adherence measures and regionally assess adherence-associated factors for the early detection of non-adherence to ART and implementation of effective intervention plans.*

Key words *HIV, AIDS, Antiretroviral therapy, Medication adherence*

[1] Hospital de Clínicas, Universidade Federal do Triângulo Mineiro (UFTM). Av. Getúlio Guaritá 130, Nossa Sra. da Abadia. 38025-440 Uberaba MG Brasil. ppcpsico@gmail.com
[2] Departamento de Psicologia, UFTM. Uberaba MG Brasil.
[3] Departamento de Nutrição, UFTM. Uberaba MG Brasil.

Introduction

The Acquired Immunodeficiency Syndrome (AIDS) emerged as a new nosological entity in the early 1980s. It is an advanced clinical manifestation of Human Immunodeficiency Virus (HIV) infection that generates severe immunodeficiency and can lead to the emergence of infections and associated neoplasms, and eventually death[1].

Due to its pandemic nature and severity, AIDS is a major global public health issue. Over the last decades, the availability of antiretroviral drugs (ARVs) has led to a significant decrease in HIV/AIDS-related morbimortality and increased quality of life of people living with the disease. The introduction of antiretroviral therapy (ART) has developed the potential of transforming AIDS into a chronic disease with possibilities for control. However, HIV/AIDS still has no cure and the effectiveness of treatment necessarily depends on lifetime adherence to ART[2].

In 2015, approximately 36.7 million people were infected with the HIV virus and 17 million had access to treatment[3]. Between 1980, onset of the epidemic in Brazil, and June 2016, 842,710 HIV/AIDS cases were registered in the country. In recent years, Brazil has reported an increased detection rate of AIDS cases among young people aged 15-24 years[4].

The initial goal of ART is not only to achieve, but also to keep viral load at undetectable levels[5-7]. Polejack and Seidl[2] point out that among the strategies to combat the epidemic worldwide, the Brazilian program for the universal and free distribution of ARVs to HIV patients, which has been in existence since 1996, under Law Nº 9.113/96[8], stands out.

Historically, in 1986, the US Food and Drug Administration approved Zidovudine for the treatment of AIDS. In Brazil, this drug was distributed in 1991. During this period, ART was based on the use of only one type of medication. As research developed further, new drugs emerged, expanding treatment options. Between 1993 and 1994, the first studies on the combination of drugs, dual ART and then triple ART became the world standard in 1996[9].

Triple ART is also known as Potent Antiretroviral Therapy or Highly Effective Antiretroviral Therapy. It is generally composed of two classes of drugs, which are separated according to their action, namely: nucleoside/nucleotide reverse transcriptase inhibitors (NRTI); non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PI); fusion inhibitors and integrase inhibitors[1,10].

In December 2013, Brazil became the first developing country and the third in the world to recommend the immediate onset of ART for all PLWHA regardless of CD4 count and viral load[11]. The country also undertook with the United Nations a commitment to the 90-90-90 goals, by which countries must achieve 90% of diagnosed PLWHA, 90% of PLWHA diagnosed for ART and 90% of PLWHA receiving ART with viral suppression[11] by 2020.

To achieve these goals, treatment adherence is necessary. Adherence to ART is a dynamic, multi-determined process under the responsibility of patients[2], with typical characteristics according to each age group[12], and the health team[5,6]. This is a complex issue, permeated by the relationship of trust and linkage between the health team and the service user[5].

Adherence to a drug involves its uptake at the prescribed dose and frequency[10], but there is no consensus as to definitions of good and poor adherence[6]. Early adherence studies described that at least 95% adherence to ART would be necessary to keep HIV viral load undetectable[13]. Glass and Cavassini[7] indicated that potent ART regimens can keep viral suppression at adherence rates below 95%. However, Rocha et al[6] point out that most studies on the subject consider that there is adherence when PLWHA use 80 to 100% of the prescribed doses.

Just as frequency of use does not count on consensus, there are many ways to verify adherence. The most commonly used methods include indirect measures, such as self-report, electronic medication monitoring, pill counts and drug withdrawal records. One direct measure is detecting ARVs or their metabolizers in the blood stream[2,5,6].

Adherence is one of the main variables in which health services can intervene to increase the effectiveness of HIV/AIDS treatment, but there are still several challenges related to this issue[2,11]. Considering its importance, it is understood that systematization of already identified factors associated with adherence is useful for reflecting on strategies for its implementation. Thus, this integrative review aims to identify in the literature factors associated with adult adherence to ART, considering the 2010-2016 period.

Ciência & Saúde Coletiva, 24(7):2543-2555, 2019

Methodology

Type of study

This is an integrative literature review aimed at synthesizing the state of knowledge related to a given subject and pointing out possible gaps that require further research[14].The research question of this study was defined based on the PICO strategy, which provides for the definition of the participant (P), intervention (I), comparison (C) and outcome(s) (O)[15]. We intend to answer the guiding question: What factors identified in the literature (O) are associated with adherence to ART (I) in adults living with HIV/AIDS (P)?

Paper selection course

Papers were selected in April 2016 for the period 2010-April 2016, and in May 2017, for the year 2016. Two independent referees conducted this search. A third referee assessed any disagreement among reviewers regarding study suitability. We searched the National Library of Medicine (Medline) via the Virtual Health Library (BVS), Latin American and Caribbean Literature in Health Sciences (Lilacs), Scientific Electronic Library Online (SciELO) and Electronic Periodicals of Psychology (PePSIC) databases. We considered Portuguese, English and Spanish papers published in the period January 2010-December 2016.

In the Lilacs, SciELO and PePSIC databases, the term "adherence" was cross-referenced with the following descriptors: HIV, AIDS, acquired immunodeficiency syndrome, high activity antiretroviral therapy, antiretroviral therapy, antiretroviral therapy and factors, and in these databases, the English and Spanish versions of the chosen terms were also searched each one at a time. In the Medline search process, due to the characteristics of this database, only English descriptors were used.

The inclusion criteria established for the selection of papers were: 1. Empirical papers that identified factors associated with ART adherence; 2. Published in English, Spanish or Portuguese; 3. That used a quantitative approach, 4. Made with PLWH with age group from 18 years and over; and 5. That were freely available for full-text reading on the Internet.

Exclusion criteria were defined as: 1. Literature review papers; 2. Theoretical studies, case reports, dissertations, theses, book chapters, consensuses, supplements or editor's comments; 3. Studies evaluating adherence interventions/strategies, programs, services and public policies related to ART adherence; 4. Works on the development and validation of scientific tools; 5. Studies addressing adherence to ART in children and adolescents living with HIV/AIDS, due to the peculiarities of access conditions to ART and typical characteristics of this age group, and 6. Studies addressing vertical HIV transmission and adherence to ART in pregnant women and postpartum women living with HIV/AIDS, due to ART's peculiarity.

To verify whether papers met the inclusion and exclusion criteria, an evaluation was performed by two independent reviewers, in the following order: (1) titles of all identified studies; (2) abstracts of selected studies in the previous phase; and (3) full-text reading of selected texts. After exclusion of papers that did not meet the inclusion criteria, a list of all the papers that composed the corpus of analysis of this study was drawn, with the following data: year and place of publication, study design, sample size, adherence measures used, levels of adherence and main factors associated with adherence.

Results

In all, 2,492 titles were identified. The database with the highest number of papers was Medline (1,528), followed by SciELO (676), Lilacs (249) and PePSIC (39). Initially, 490 studies were excluded because they were duplicated. Then, 1,675 paper were excluded, mainly because studies did not address factors associated with ART adherence (1,211). Therefore, 327 articles remained for full-text reading. Of these publications, 164 were retrieved for free full-text reading, and after that reading, 39 publications were excluded, totaling 125 papers that composed the corpus of the work. Figure 1 shows the flowchart of the selection strategy of studies according to PRISMA standards[16].

Characteristics of studies

The year with the highest number of published studies was 2011 (19.2%). Table 1 shows a wide geographical distribution in the developed studies; however, almost half of the studies were conducted in North America (n = 61, 48.8%), of which 56 were in the United States. Thirteen studies were published in Brazil. It is noteworthy that four papers were developed in more than one country[17-20].

Regarding sample size, most of the studies (56.8%) were performed with a range of 101 to 500 participants and only 2 (2.6%) had a sample size of less than 50. The survey with the smallest sample size was that of Keuroghlian et al.[21], with 43 participants, and the survey with the largest sample size was that of Murphy et al.[22], with 14,128 participants.

The groups of people who composed the sample varied in the papers analyzed. There was one work with people over 50 years of age[23], one with PLWHA with TB-coinfection[24], three with people starting ART[25-27], five with illicit drug users[28-32], six with women, as in the work of Jones et al.[33], and six with men, exemplified in the study by Knowlton et al.[34]. Among the studies analyzed, 72 (57.6%) were cross-sectional, as in Silva et al.[27], 50 (40%) were longitudinal, including a prospective cohort study, as in Lee et al.[30], and retrospective, as in Scott-Sutton et al.[35], and three (2.4%) case-control, as in Rego et al.[36].

Definition and measures of adhesion

The cutoff point established for adherence ranged from 75% to 100% of the use of prescribed medication doses, with adherence limited to 95% for 45 (36.0%) reviewed studies. Five studies defined adherence considering different sub-levels[35,37-40]. For example, Kalichman et al.[38] considered fair adherence (75% of medication use), good (85%) and optimal (95%). Two studies defined adherence in days of delay in the withdrawal of medication from the pharmacy[26,41].

Some 81.6% of studies used only one method to measure adherence. Among the adherence measures used, most studies used self-report on medication use for a period (70.4%). Studies that used this measure inquired about the use of medication with varying durations, between 24 hours and 9 months. Some papers chose to use self-report in different periods of time in order to reduce memory bias. One of these studies was that

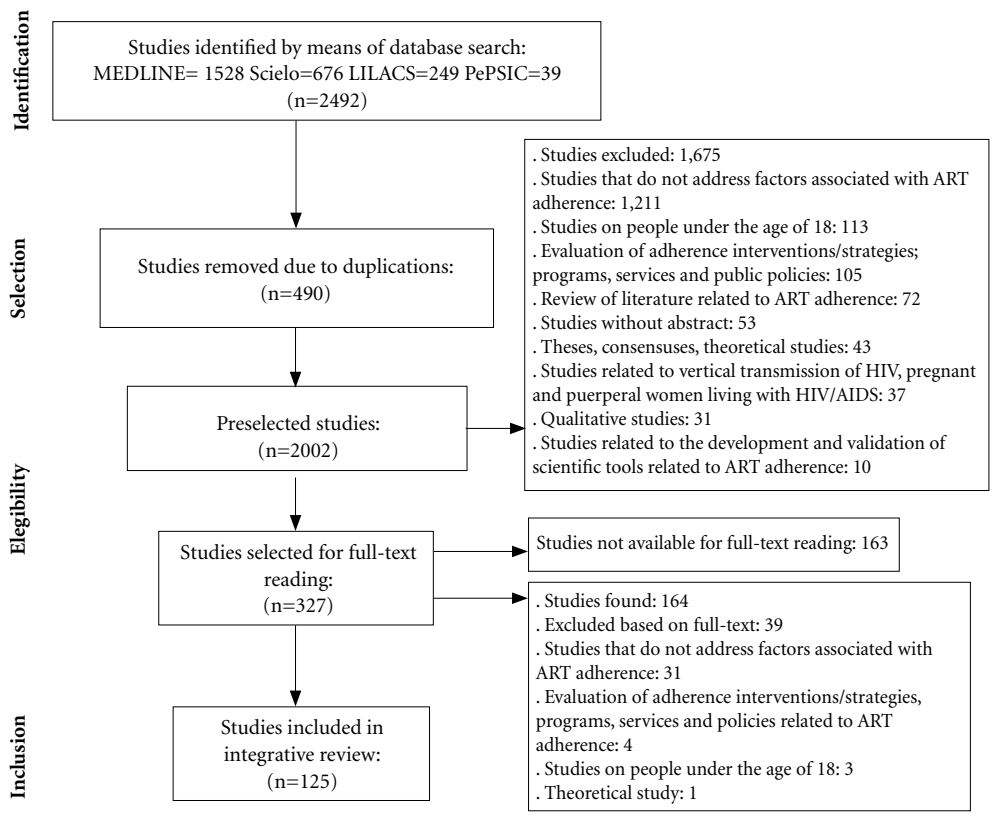

Figure 1. Flowchart of the selection of studies according to PRISMA.

Ciência & Saúde Coletiva, 24(7):2543-2555, 2019

Table 1. Distribution of 125 papers analyzed according to selected variables.

Study characteristics	N	%
Year of publication		
2010	17	13.6
2011	24	19.2
2012	19	15.2
2013	16	12.8
2014	20	16.0
2015	16	12.8
2016	13	10.4
Location		
Africa	22	17.6
North America	61	48.8
Latin America	21	16.8
Asia	11	8.8
Europe	9	7.2
Multi-continental	1	---
Study sampling size		
≤ 50 participants	2	1.6
51 to 100 participants	15	12.0
101 to 500 participants	71	56.8
501 to 1,000 participants	15	12.0
1,001 to 10,000 participants	21	16.8
> 10,001 participants	1	---
Design		
Cross-sectional	72	57.6
Longitudinal	50	40.0
Case-control	3	2.4
Use of adherence measures		
Use of 1 measure	102	81.6
Use of 2 measures	20	16.0
Use of 3 measures	3	2.4
Adherence measures		
Self-report	88	70.4
Dispensing at the pharmacy	25	20.0
Tablet counting	19	15.2
Electronic device (MEMS)	17	13.6
Viral load	2	1.6
Recording in medical records	2	1.6
Adherence measure cutoff point		
100%	14	11.2
95%	45	36.0
90%	13	10.4
< 90%	3	2.4
Not provided	50	40.0

of Lehavot et al.[42], who evaluated adherence considering 2 weeks and 3, 6 and 9 months, assessed with the Simplified Medication Adherence Questionnaire (SMAQ). While study by Dagli-Hernandez et al.[43] used two self-report measures, namely, SMAQ and CEAT-HIV ART Adherence Assessment Questionnaire.

Among the validated self-report scales and questionnaires, the most used adherence measurement tools were the Adults AIDS Clinical Trials Group (n = 17), used in the research by Bianco et al.[23], followed by the Visual Analogue Scale (VAS) (n = 13), used by Murphy et al.[22], CEAT-HIV (n = 7), used by Dagli-Hernandez et al.[43] and SMAQ (n = 6), used by Knowlton et al.[34]. The Center for Adherence Support Evaluation Index, used by Morojele et al.[44] and the Morisky Medication Adherence Scale, used for example by Kader et al.[45] were used in three studies each. The Questionnaire on Psychological Variables and Adherence Behaviors (VPAD-21) was used only in one study[46].

The second most commonly used measure of adherence was the pharmacy dispensing record (n = 25, 20%), used by Fonseca et al[41], followed by tablet count (n = 19, 15.2%), employed, for example, by Yaya et al.[47] and by the electronic medication monitoring device. This device is placed on the medication's bottle cap and was used in 17 surveys, such as that of Knowlton et al.[34], all conducted in the U.S. Other measures included undetectable viral load (n = 2), used by Dagli-Hernandez et al.[43] and medical record (n=2), used by Silva et al.[27].

Twenty-three studies (18.4%) used more than one adherence measure, but with some variations. An example was that of Silva et al.[27], who used data collected in medical records and records at the pharmacy as adherence measures. While study by Yaya et al.[47] assessed adherence using self-report, pill counts and prescription renewal rates for three months.

Level of adherence

Among the studies analyzed, 68.8% showed the level of adherence. The lowest adherence was 20%, identified in the study by Cedillo et al.[48]. This work was conducted in Mexico and examined the relationship between some mental diseases indicators and therapeutic adherence. The highest adherence level was reported by Sumari-de-Boer et al.[49] with ethnic minorities in the Netherlands and Dutch immigrants, assessing adherence through self-report and pharmacy dispensing. According to the self-report measure, authors observed an adherence of 96% for immigrants and 99% for ethnic minorities, while pharmacy dispensing showed 89% adherence of immigrants and 95% among ethnic minorities.

The level of adherence varies between countries. For example, an adherence rate of 78.4% was found in Togo[47], while in the U.S., Knowlton et al[34] reported an adherence rate of 83%. This variation was observed even within the same country, as seen in different studies carried out in Mexico, where rates of 20%[48], 47%[50] and 68% adherence were observed[46].

Adherence-associated factors

Around 64.8% of studies sought to explore the relationship of a single factor with adherence, while the remainder aimed to identify multiple factors related to adherence. Variables associated to adherence were grouped into five categories, based on the main results of the 125 papers analyzed, namely: 1. Individual variables; 2. Treatment characteristics; 3. Characteristics of HIV/AIDS infection; 4. Relationship with health services; and 5. Social support. These factors are summarized in Table 2, which also contains examples of studies that addressed the referred factors investigated. We reiterate that papers quoted as examples may have other important results, in addition to the underscored.

Individual variables

This category included variables related to participant characterization factors, such as age, gender, skin color/ethnicity/demographic group, schooling, employment status, income, marital status, housing, food insecurity and syndemia i.e. multiple interconnections between health and psychosocial conditions. Also included are lifestyle (use of vitamin C, physical exercise, quality of sleep and use of cellphone reminders), neuropsychological aspects and spirituality and religiosity, considering spirituality as an existential intimate feeling of search for the meaning of life and being in the world and religiosity as a set of beliefs and practices belonging to a doctrine, shared by a group of people[51].

The influence of gender is highlighted, showing contradictory relationships. For example, some studies have indicated that women would have lower adherence[32], while others indicated that being a man would be a factor of low adherence[52]. Skin color/ethnicity/demographic group was also frequently associated with adherence. In the reviewed studies, the skin color black[53] and low income were associated with low compliance[53].

Individual variables also include factors related to the use of licit drugs (alcohol, amphetamines, drugs and tobacco abuse) and use of illicit drugs. It is worth mentioning the use of alcohol, which was cited as a relevant predictor of non-adherence in 14 studies, such as Rego et al.[36].

Psychological variables also appeared as a significant factor associated with adherence, and are divided into negative psychological variables, which were predictors of low adherence, and positive, which facilitated adherence. Among negative variables are psychic distress, anxiety, stress, suffering violence and evidence of depressive, panic, posttraumatic stress disorders and pain catastrophization. Positive psychological variables include self-efficacy, attitude/motivation, personal beliefs, coping/resilience and quality of life.

Antiretroviral treatment

Among the variables related to antiretroviral treatment, the following are indicated: medication regimen; adverse effects; forgetfulness, being away from home; sleeping at the time of medication; time of ART use; lack of ART; strategy to remember ART; time between first ART and the diagnosis of HIV and the cost of ART. The simplification of ART, that is, reduced number of pills resulted in improved adherence[18], and there was greater adherence in single pill use compared to the same regimen more than once per day[60].

HIV/AIDS infection

Among the variables related to HIV/AIDS, the factors associated with adherence were: time of diagnosis; general health conditions, both good and bad; dissemination of the serological status, that is, other people know about the retrovirus diagnosis; knowledge about HIV and ART and having family members living with HIV. We can observe that there were studies in which the longest time of diagnosis was related to better adherence rates[61], while in other studies adherence decreased over the time of diagnosis of HIV/AIDS[57], which shows that adherence can have different relationships with the same variable, depending on the population surveyed.

Health services

In relation to health services, the availability of a multidisciplinary team, receiving home visits, shorter time interval between consultations, shorter distance from the consultation site, availability of specialized pharmacies, satisfaction

Ciência & Saúde Coletiva, 24(7):2543-2555, 2019

Table 2. Categories and variables associated with ART adherence.

Categories and variables	Sample examples	Frequency (n) of the variable in the results of papers analyzed
1. Individual characteristics		
Sociodemographic characteristics	Bonolo et al. (2013)[25]; Simoni et al. (2012)[53].	
Gender		12
Skin color/ethnicity/demographic group		11
Age		10
Schooling		7
Employment relationship/income/ economic level		5
Marital status		3
Housing		2
Food insecurity		5
Syndemia		2
Use of licit drugs	Rego et al. (2011)[7].	18
Use of illicit drugs	Blashill et al.(2012)[31].	9
Negative psychological variables	Cedillo et al.(2011)[48].	25
Positive psychological variables	Nokes et al. (2014)[17].	15
Neuropsychological aspects	Kelly C.M. et al. (2014)[54].	6
Lifestyle	Tran B et al.(2013)[55].	5
Spirituality and religiosity	Kisenyi et al.(2013)[56].	3
2. Antiretroviral treatment	Langebeek et al.(2014)[18]; Scott-Sutton et al.(2016)[35].	
Medication scheme		13
Adverse effects		12
Forgetfulness, being away from home and sleeping at the time of medication		9
Time of use of ART		7
Lack of ART		2
Strategy to remember ART		2
ART cost		1
Time between first ART and HIV diagnosis		1
3.HIV/AIDS infection	Wilson et al.(2013)[57]; Nelsen et al. (2013)[58].	
Diagnosis time		5
General health conditions		5
Other people know about the diagnosis		3
Knowledge about HIV and ART		2
Having a family member with HIV		1
4. Health services	Murphy et al.(2012)[22].	
Multidisciplinary team available		1
Receiving home visits		1
Time interval between consultations		1
Distance from consultation location		1
Specialized pharmacies		1
Care satisfaction		1
Relationship between professionals and users of health services		2
5. Social support	Kelly J.D. et al. (2014)[59].	9

with care and good relationship between professionals and users of health services, with emphasis on quality of the therapeutic relationship and agreement between doctor/patient were associated with better adherence rates. These results point to the importance of a multidisciplinary and medical team integrated in the services of reference for early detection of non-adherence[5].

Social support

In this review, social and family support was a significant factor associated with adherence to ART. This factor was investigated in studies such as Kelly et al.[59]. Social and affective support was pointed out as a means to improve adherence, although it is not enough to ensure a successful treatment, requiring a combination of multiple factors[59].

Discussion

This integrative literature review pointed out that non-adherence occurs universally and is observed in both developed and developing countries. It also showed that adherence might vary within the same country or from one region to another, evidencing the heterogeneous aspect of HIV/AIDS infection, adherence to ART and associated factors. According to results, non-adherence rates ranged from 1% to 80%[48,49].

Among the measures of adherence, the use of single (81.6%) and subjective measures predominated, since 70.4% of the studies used self-report. Self-report's advantages are low cost and short application time[43]. However, its use raises some questions, considering that its results tend to be less accurate[43]. According to Polejack and Seidl[2], the wide variety of methods for assessing adherence according to self-report may hinder the comparison of outcomes between surveys. In their study, Dagli-Hernandez et al.[43] evaluated which indirect adherence evaluation method better reflects ART's effectiveness, comparing three adherence measuring methods, namely, viral load, pharmacy drug dispensing and two measures of validated self-report (SMAQ and CEAT-HIV). This research suggested the combination of two gauging methods as the best way to assess adherence and recommended the use of the viral load test and the CEAT-HIV adherence questionnaire.

The use of 7 validated self-report scales / questionnaires were observed, which indicates a progress, since the use of validated tools allows a better comparison of results and more reliable data. It should be noted that electronic monitoring is still uncommon in developing countries, a fact that has already been observed in the reviews of Bonolo et al.[5] and Rocha et al.[62], and can be explained by the high cost of this tool.

A great variability of the levels of adherence found are noted, mainly due to the definition of adherence, type of measurement and cut-off point. According to the established adherence cutoff point, it varied between 75% and 100% of the use of the prescribed medication doses. Given this variability, it is difficult to interpret whether adherence depends on the population studied or whether it is related to the great methodological distinction of the studies. Thus, the definition of a single adherence measure, composed of two measurement methods, could increase the comparability of the studies and ensure measure's reliability.

In this study, multiple factors associated with ART adherence were identified through individual variables, treatment characteristics, characteristics of the infection, aspects of the relationship with health services and social support. It is worth noting that, in view of these variables, adherence assumed different values and relationships, depending on the population studied[57,61], confirming the heterogeneous and regional character of adherence-related factors.

It is important to highlight that individual variables related to the person under treatment, which is inserted in a socio-historical and cultural context. Thus, these variables are traversed by sociocultural issues. Within this category, sociodemographic factors[53] were important predictors of non-adherence, showing association of low adherence with greater social vulnerability[53]. Ayres et al.[63] say that social vulnerability expresses a set of individual, collective and contextual illness-predisposing aspects. Such predisposition stems from reduced access to adequate resources to protect themselves. This realm of ART adherence deserves a close look of national and international pandemic public policy programs.

Also in the individual variable category, a gap was identified in the studies on adherence with specific populations. We found only one study with the elderly and no studies with young adults. In this context, it is worth noting that, in Brazil, the rate of HIV/AIDS detection has increased in this age group[4]. Likewise, studies on adherence with heterosexuals and men who have sex with other men were found, but no research

was found on adherence to treatment with women who have sex with other women. Pinto et al.[64] point out the scarce volume of studies on sexual risk behavior in lesbians and reiterates that, while there is a low risk of HIV transmission among women who have sex with other women, the possibility is there and transmission can occur with the exchange of vaginal secretions, through the practice of sex during the menstrual period, as well as through shared unprotected sexual accessories.

It is also worth noting that the use of cell phone reminders has been associated with better adherence rates[55]. In this review, this variable was included in lifestyle, although it should be considered that in many countries and for many people, having a cell phone is not an option, due to its high cost. Nevertheless, many interventions have been studied with the use of mobile communication technologies to support adherence, as in the study by Rodrigo et al.[65] carried out in Indiato analyze the cost of this type of intervention, in which it was concluded that the cost is low and is facilitated by the low cost of mobile communication in the country. The importance of critical reviews and empirical studies on interventions and strategies to improve antiretroviral adherence rates is underscored.

In the category of ART, studies have shown that the simplified antiretroviral regimens with a single tablet favored adherence[18,35]. However, while Brazil has been distributing the combined triple scheme in a single drug since 2014[10], in this review, no studies with this theme were found in the country.

The review did not include all existing databases and did not investigate adherence in children and adolescents or in pregnant and postpartum women. Nevertheless, studies analyzed suggest the importance of constant monitoring and evaluation of adherence to ART, its associated factors and offering comprehensive care to PLWHA. The early detection of non-adherence allows the establishment of timely interventions, increasing the quality of life of this population.

Final considerations

The literature review allowed the identification of multiple factors associated with adherence, pointing to the complexity of the issue and the need for constant investigations in this area, taking into account its socio-historical and cultural realms. In addition to affecting individual health, adherence to ART is associated with the potential collective transmission of HIV/AIDS infection. Critical reviews and empirical studies on interventions and strategies to improve adherence could overly contribute to academic and technical areas, as well as to the population in general, due to the importance of early detection of the risk of non-adherence and of establishing individual and collective care strategies for PLWHA according to the demands and needs of the users of each service.

The analysis of papers showed that it is necessary to concentrate actions to identify the levels of adherence in different countries, including in the investigations the identification of adherence-associated factors. These factors vary across different regions, and it is necessary to consider the characteristics of people with HIV/AIDS, the treatment they receive, the services they attend and the emotional and social support they receive. Moreover, the difficulty of comparing study results due to methodological differences reveals the need for the definition of a gold standard measure for adherence, allowing a comparison of the prevalence identified in different investigations and regions/countries.

Based on these considerations, we highlight the importance of health services in their work of characterizing the profile, knowing the factors associated with the adherence of its users and systematizing measures that favor adherence. Investments are urgently required in public policies focused on adherence to ART, ranging from the training of health teams and services infrastructure to social security actions that benefit the entire population, including health, education, housing and fight against HIV/AIDS prejudice and stigma related to the infection.

Collaborations

PP Carvalho: worked on designing the project, collecting and analyzing data, interpreting the results and writing the text; SM Barroso and FRO Penaforte: worked on the design of the project, critically reviewed and approved the final version of the article; HC Coelho: worked on data collection, as second judge in the selection of articles and assisted in the writing of the article.

References

1. Maich IF. *Avaliação da flexibilidade cognitiva em adultos com HIV* [dissertação]. Curitiba: Universidade Federal do Paraná; 2012.
2. Polejack L, Seidl EMF. Monitoramento e avaliação da adesão ao tratamento antirretroviral para HIV/AIDS: desafios e possibilidades.*Cien Saude Colet* 2010; 15(Supl. 1):1201-1208.
3. Jointed United Nations Programme on HIV/AIDS. *Global AIDS Uptade 2016*. [acessado 2017 Abr 20]. Disponível em: http://www. unaids.org/sites/default/files/media_asset/global- AIDS-update-2016_en.pdf
4. Brasil. Ministério da Saúde (MS). *Boletim Epidemiológico – AIDS*. Brasília: MS; 2016.
5. Bonolo P, Gomes RRFM, Guimarães MD. Adesão à terapia anti-retroviral (HIV/AIDS): fatores associados e medidas da adesão. *Epidemiol Serv. Saúde* 2007; 16(4):267-278.
6. Rocha GM, Machado CJ, Acurcio FA, Guimarães MDC. Monitoring adherence to antiretroviral treatment n Brazil: an urgent challenge. *Cad Saude Publica* 2011; 27(Supl. 1):67-78.
7. Glass T, Cavassini M. Asking about adherence - from flipping the coin to strong evidence. *Swiss Med Wkly* 2014; 144:14016.
8. Brasil. Lei n° 9.313, de 13 de novembro de 1996. Dispõe sobre a distribuição gratuita de medicamentos aos portadores do HIV e doentes de AIDS. *Diário Oficial da União* 1996; 13 nov.
9. Rossi SMG, Maluf ECP, Carvalho DS, Ribeiro CEL, Battaglin CP. Impacto da terapia antirretroviral conforme diferentes consensos de tratamento de AIDS no Brasil. *Rev. Panam Salud Publica* 2012; 32(2):117-123.
10. Brasil. Ministério da Saúde (MS). *Protocolo clínico e diretrizes terapêuticas para o manejo da infecção pelo HIV em adultos.* Brasília: MS; 2013.
11. Brasil. Ministério da Saúde (MS). *Boletim Epidemiológico – AIDS*. Brasília: MS; 2014.
12. Guerra CPP, Seidl EMF. Crianças e adolescentes com HIV/AIDS: revisão de estudos sobre revelação do diagnóstico, adesão e estigma. *Paideia* 2009; 19(42):59-65.
13. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener MM, Singh N. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern. Med.* 2000; 133(1):21-30.
14. Mendes KDS, Silveira RCCP, Galvão CM. Revisão integrativa: método de pesquisa para a incorporação de evidências na saúde e na enfermagem. *Texto & Contexto Enferm* 2008; 17(4):758-764.
15. Harris JD, Quatman E, Manring MM, Siston, RA, Flanigan DC. How to write a systematic review. *Am J Sports Med* 2014; 42(11):2761-2768.
16. Galvão TF, Pansani TSA, Harrad D. Principais itens para relatar Revisões sistemáticas e Meta-análises: A recomendação PRISMA. *Epidemiol. Serv. Saúde* 2015; 24(2):335-342.
17. Nokes K, Johnson MO, Webel A, Rose CD, Phillips J C, Sullivan KS, Tyer-Viola L, Rivero-Méndez M, Nicholas P, Kemppainen J, Sefcik E, Chen WT, Brion J, Eller L, Kirksey K, Wantland D, Portillo C, Corless IB, Voss J, Iipinge S, Spellmann M, Holzemer WL. Focus on increasing treatment self-efficacy to improve human immunodeficiency virus treatment adherence. *J Nurs Scholars* 2012; 44(4):403-410.
18. Langebeek N, Sprenger HG, Gisolf EH, Reiss P, Sprangers MAG, Legrand JC, Richter C, Nieuwkerk PT. A simplified combination antiretroviral therapy regimen enhances adherence, treatment satisfaction and quality of life: results of a randomized clinical trial. *HIV Med* 2014; 15(5):286-290.
19. Safren SA, Mayer KH, Ou SS, McCauley M, Grinsztejn B, Hosseinipour MC, Kumarasamy N, Gamble T, Hoffman I, Celentano D, Chen YQ, Cohen MS. Adherence to Early Antiretroviral Therapy: Results From HPTN 052, a Phase III, Multinational Randomized Trial of ART to Prevent HIV-1 Sexual Transmission in Serodiscordant Couples. *J Acqui Immune Defic Syndr* 2015; 69(2):234-240.
20. Koole O, Denison JA, Menten J, Tsui S, Wabwire-Mangen F, Kwesigabo G, Mulenga M, Auld A, Agolory S, Mukadi YD, van Praag E, Torpey K, Williams S, Kaplan J, Zee A, Bangsberg DR, Colebunders R. Reasons for Missing Antiretroviral Therapy: Results from a Multi-Country Study in Tanzania, Uganda, and Zambia. *PLoS One* 2016; 11(1):e0147309.
21. Keuroghlian AS, Kamen CS, Neri E, Lee S, Liu R, Gore-Felton C. Trauma, dissociation, and antiretroviral adherence among persons living with HIV/AIDS. *J Psychiatr Res* 2011; (7):942-948.
22. Murphy P, Cocohoba J, Tang A, Pietrandoni G, Hou J, Guglielmo BJ Impact of HIV-specialized pharmacies on adherence and persistence with antiretroviral therapy. *AIDS patient care and STDs* 2012; 26(9):526-531.
23. Bianco JA, Heckman TG, Sutton M, Watakakosol R, Lovejoy T. Predicting adherence to antiretroviral therapy in HIV-infected older adults: the moderating role of gender. *AIDS Behav* 2011; 15(7):1437-1446.
24. Lemos LA, Fiuza MLT, Reis RK, Ferrer AC, Gir E, Galvão MTG. Adherence to antiretrovirals in people coinfected with the human virus and tuberculosis. *Rev Latino-Am Enfermagem* 2016; 24:e2691.
25. Bonolo P, Ceccato MDGB, Rocha GM, Assis Acúrcio F, Campos LN, Guimarães MDC. Gender differences in non-adherence among Brazilian patients initiating antiretroviral therapy. *Clinics* 2013; 68(5):612-620.
26. Buscher A, Hartman C, Kallen MA, Giordano TP. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, antiretroviral-naive HIV patients. *Int J STD AIDS* 2012: 23(5):351-355.
27. Silva JAG, Dourado I, Brito AMD, Silva CALD. Factors associated with non-adherence to antiretroviral therapy in adults with AIDS in the first six months of treatment in Salvador, Bahia State, Brazil. *Cad Saude Publica* 2015; 31(6):1188-1198.

28. Milloy MJ, Kerr T, Buxton J, Rhodes T, Guillemi S, Hogg R, Montaner J, Wood E. Dose-response effect of incarceration events on nonadherence to HIV antiretroviral therapy among injection drug users. *J Infect Dis* 2011; 203(9):1215-1221.
29. Newville H, Berg KM, Gonzalez JS. The interaction of active substance use, depression, and antiretroviral adherence in methadone maintenance. *Int J Behav Med* 2015; 22(2):214-222.
30. Lee WK, Milloy MJ, Walsh J, Nguyen P, Wood E, Kerr T. Psychosocial factors in adherence to antiretroviral therapy among HIV-positive people who use drugs. *Health Psychol*. 2016; 35(3):290-297.
31. Blashill AJ, Gordon JR, Safren SA. Appearance concerns and psychological distress among HIV-infected individuals with injection drug use histories: Prospective analyses. *AIDS patient care and STDs* 2012; 26(9):557-561.
32. Tapp C, Milloy MJ, Kerr T, Zhang R, Guillemi S, Hogg RS, Montaner J, Wood E. Female gender predicts lower access and adherence to antiretroviral therapy in a setting of free healthcare. *BMC Infect Dis* 2011; 11:86.
33. Jones AS, Lillie-Blanton M, Stone VE, Ip EH, Zhang Q, Wilson TE, Cohen MH, Golub ET, Hessol NA. Multi-dimensional risk factor patterns associated with non-use of highly active antiretroviral therapy among human immunodeficiency virus-infected women. *Women's Health Issues* 2010; 20(5):335-342.
34. Knowlton AR, Yang C, Bohnert A, Wissow L, Chande RG, Arnsten JA. Informal care and reciprocity of support are associated with HAART adherence among men in Baltimore, MD, USA. *AIDS Behav* 2011; 15(7):1429-1436.
35. Scott-Sutton S, Magagnoli J, Hardin JW. Impact of Pill Burden on Adherence, Risk of Hospitalization, and Viral Suppression in Patients with HIV Infection and AIDS Receiving Antiretroviral Therapy. *Pharmacotherapy* 2016; 36(4):385-401.
36. Rego SRM, Oliveira CFA, Rego DMS, Santos JRF, Silva VB. Estudo do autorrelato de adesão e uso problemático de álcool em uma população de indivíduos com AIDS em uso de HAART. *J Bras Psiquiatr* 2011; 60(1):46-49.
37. Kalichman SC, Washington C, Grebler T, Hoyt G, Welles B, Merely C, Kalichman MO, Cherry C. Treatment outcomes among people living with HIV Who are food insecure and prescribed antiretrovirals taken with food. *J Prim Carer Community Health* 2015; 6(1):35-40.
38. Kalichman SC, Cherry C, Amaral C, White D, Kalichman MO, Pope H, Swetsze C, Jones M., Macy R. Health and treatment implications of food insufficiency among people living with HIV/AIDS, Atlanta, Georgia. *J Urban Health* 2010; 87(4):631-641.
39. Venkatesh KK, Srikrishnan AK, Mayer KH, Kumarasamy N, Raminani S, Thamburaj E, Prasad L, Triche EW, Solomon S, Safren SA. Predictors of non adherence to highly active antiretroviral therapy among HIV-infected South Indians in clinical care: implications for developing adherence interventions in resource-limited settings. *AIDS patient care and STDs* 2010; 24(12):795-803.
40. Becker BW, Thames AD, Woo E, Castellon SA, Hinkin CH. Longitudinal change in cognitive function and medication adherence in HIV-infected adults. *AIDS Behav* 2011; 15(8):1888-1894.
41. Fonseca LCD, Martins FJ, Vieira RDCPA, Pereira RMC, Ferreira AS, Raposo NRB. Evaluation of inadequate anti-retroviral treatment in patients with HIV/AIDS. *Rev. Socied. Bras. Med. Trop.* 2012; 45(2):151-155.
42. Lehavot K, Huh D, Walters KL, King KM, Andrasik, MP, Simoni JM. Buffering effects of general and medication-specific social support on the association between substance use and HIV medication adherence. *AIDS Patient care and STDs* 2011; 25(3):181-189.
43. Dagli-Hernandez C, Lucchetta RC, Nadai TR, Galduróz JCF, Carvalho Mastroianni P. Self-perception of knowledge and adherence reflecting the effectiveness of antiretroviral therapy. *Patient Prefer Adherence* 2016; 10:1787-1793.
44. Morojele NK, Kekwaletswe CT, Nkosi S. Associations between alcohol use, other psychosocial factors, structural factors and antiretroviral therapy (ART) adherence among South African ART recipients. *AIDS Behav* 2014 Mar; 18(3):519-524.
45. Kader R, Govender R, Seedat S, Koch JR, Parry C. Understanding the Impact of Hazardous and Harmful Use of Alcohol and/or Other Drugs on ARV Adherence and Disease Progression. *PLoS One* 2015; 10(5):e0125088.
46. Ramírez MTG, López JAP. Motivos, apoyo social y comportamientos de adhesiónen personas con VIH: modelamiento conecuaciones estructurales. *Universitas Psychologica* 2011; 10(2):399.
47. Yaya I, Landoh DE, Saka B, Wasswa P, Aboubakari AS, N'Dri MK, Patassi AA, Kombaté K, Pitche P. Predictors of adherence to antiretroviral therapy among people living with HIV and AIDS at the regional hospital of Sokodé, Togo. *BMC Public Health* 2014; 14(1):1.

48. Cedillo IG, Castro FA, Delgado MR, Cappello OSA. Indicadores de enfermedades mentales en pacientes mexicanos con VIH/SIDA y surelación con la a dherencia terapéutica. *Actualidades en psicología* 2011; 25(112):37-55.
49. Sumari-de Boer IM, Sprangers MA, Prins JM, Nieuwkerk PT. HIV stigma and depressive symptoms are related to adherence and virological response to antiretroviral treatment among immigrant and indigenous HIV infected patients. *AIDS Behav* 2012; 16(6):1681-1689.
50. Piña JA, Sánchez-Sosa JJ, Fierros LE, Ybarra JL, Cázares Ó. Variables psicológicas y adhesiónen personas con VIH: evaluación en función del tiempo de infección. *Terapia psicológica* 2011; 29(2):149-157.
51. Murakami R, Campos CJG. Religião e saúde mental:desafio de integrar a religiosidade ao cuidado com o paciente. *Revista Brasileira de Enfermagem* 2012; 65(2):361-367.
52. Eyassu MA, Mothiba TM, Mbambo-Kekana NP. Adherence to antiretroviral therapy among HIV and AIDS patients at the Kwa-Thema clinic in Gauteng Province. *Afr. J Prim Health Care Fam. Med* 2016; 8(2):1-7.
53. Simoni JM, Huh D, Wilson IB, Shen J, Goggin K, Reynolds NR, Remien RH, Rosen MI, Bangsberg DR, Liu H. Racial/ethnic disparities in ART adherence in the United States: findings from the MACH14 study. *J Acquir Immune Defic Syndr* 2012; 60(5):466.
54. Kelly CM, van Oosterhout JJ, Ngwalo C, Stewart RC, Benjamin L, Robertson KR, Khoo S, Allain TJ, Solomon T. HIV associated neurocognitive disorders (HAND) in Malawian adults and effect on adherence to combination anti-retroviral therapy: a cross sectional study. *PLoS One* 2014; 9(6):e98962.
55. Tran BX, Nguven LT, Nguven OL, Hoang OV, Hwang J Determinants of antiretroviral treatment adherence among HIV/AIDS patients: a multisite study. *Glob Health Action* 2013; 6: 10.3402.
56. Kisenyi RN, Muliira JK, Ayebare E. Religiosity and adherence to antiretroviral therapy among patients attending a public hospital-based HIV/AIDS clinic in Uganda. *J Relig Health* 2013; 52(1):307-317.
57. Wilson IB, Bangsberg DR, Shen J, Simoni JM, Reynolds NR, Goggin K,Gross R, Arnsten JH, Remien RH, Erlen JA Liu, H. Heterogeneity among studies in rates of decline of ART adherence over time: Results from the MACH14 study. *J Acquir Immune Defic Syndr* 2013; 64(5):448.
58. Nelsen A, Gupta S, Trautner BW, Petersen NJ, Garza A, Giordano TP, Naik AD, Rodriguez-Barradas MC. Intention to adhere to HIV treatment: a patient-centred predictor of antiretroviral adherence. *HIV Med* 2013; 14(8):472-480.
59. Kelly JD, Hartman C, Graham J, Kallen MA, Giordano, TP. Social support as a predictor of early diagnosis, linkage, retention, and adherence to HIV care: results from the steps study. *J Assoc. Nurses AIDS Care* 2014; 25(5):405-413.
60. Bangsberg, DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS* 2010; 24(18):28-35.
61. Maqutu D, Zewotir T, North D, Naidoo K, Grobler A. Determinants of optimal adherence over time to antiretroviral therapy amongst HIV positive adults in South Africa: a longitudinal study. *AIDS Behav* 2011; 15(7):1465-1474.
62. Rocha GM, Bonolo PF, Ceccato MGB, Campos LN, Gomes RRFM, Acúrcio FA, Guimarães MDC. Adesão ao tratamento antirretroviral: Uma revisão sistemática, 2004-2009. In: Guimarães MDC, Acúrcio FA, Machado JM, organizadores. *Adesão ao Tratamento Antirretroviral no Brasil: Coletânea de Estudos do Projeto ATAR.* Brasília: Editora MS; 2010. Série B. Textos Básicos de Saúde. Série: Pesquisas, Estudos e Avaliação nº XX. p. 17.
63. Ayres JCRM, Calazans GJ, França Júnior I, Saletti- Filho HC. O conceito de vulnerabilidade e as práticas de saúde: novas perspectivas e desafios. In: Czeresnia D, Freitas C M. *Promoção da saúde*: *conceitos, reflexões, tendências*. Rio de Janeiro: Fiocruz; 2003. p. 117-139.
64. Pinto VM, Tancredi MV, Neto AT, Buchalla CM. Sexually transmitted disease/HIV risk behaviour among women who have sex with women. *Aids* 2004; 19(Supl. 4):64-69.
65. Rodrigues R, Bogg L, Shet A, Kumar DS, De Costa A. Mobile phones to support adherence to antiretroviral therapy: what would it cost the Indian National AIDS Control Programme? *J Int AIDS Soc* 2014; 17:19036.

Article submitted 24/07/2017
Approved 19/10/2017
Final version submitted 21/10/2017