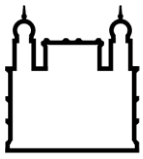

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JESSICA DE MATTOS COSTA

ADESÃO À TERAPIA ANTIRRETROVIRAL PARA HIV/AIDS NA AMÉRICA LATINA E CARIBE: UMA REVISÃO SISTEMÁTICA E METANÁLISE

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Dedico este trabalho ao meu querido avô, saudoso e eterno incentivador,

Nilo Baptista de Mattos Júnior.

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Ao INI (Instituto Nacional de Infectologia Evandro Chagas) por me acolher como aluna.

RESUMO

Objetivo: Sintetizar quantitativamente a literatura publicada com revisão por pares, apresentando uma estimativa combinada de adesão ao tratamento antirretroviral (TAR) por pessoas vivendo com HIV (PVHIV) na América Latina e Caribe (ALC); sintetizar qualitativamente os métodos utilizados para mensurar a adesão à TAR e descrever os fatores associados à baixa adesão entre os estudos selecionados.

Métodos: Foi realizada uma busca eletrônica na literatura publicada até julho de 2016 nos portais do PubMed, Web of Science e Biblioteca Virtual em Saúde (BVS), abrangendo as seguintes bases de dados: MEDLINE, LILACS, PAHO e IBECS. Dois revisores independentes selecionaram e extraíram dados sobre a adesão ao tratamento e características dos estudos. A estimativa combinada da adesão foi estimada usando um modelo de efeitos aleatórios. O risco de viés em estudos individuais foi avaliado por dois investigadores utilizando a ferramenta de Avaliação de Risco de Viés para Estudos Não-Aleatórios (RoBANS).

Resultados: A meta-análise incluiu 53 estudos publicados entre 2005 e 2016, que analisaram 22.603 PVHIV em 25 países da ALC. A adesão agregada na ALC foi de 70% (IC 95%: 63-76; I^2 = 98%), semelhante aos níveis identificados por estudos realizados em regiões em desenvolvimento. A análise de subgrupos mostrou que a proporção de adesão foi maior no menor período de avaliação da adesão e nos países de menor nível de renda, renda per capita e Índice de Desenvolvimento Humano (IDH). O autorrelato do indivíduo foi o método mais utilizado. Estudos relataram diversas barreiras para a adesão, como abuso de álcool e substâncias psicoativas, depressão, desemprego e número de comprimidos diários.

Conclusão: O nosso estudo sugere que a adesão à TAR na ALC pode estar abaixo dos níveis necessários para assegurar supressão a longo prazo da carga viral.

Palavras-chave: Fármacos Anti-HIV; Terapia Antirretroviral de Alta Atividade; Adesão à Medicação; Países em Desenvolvimento; América Latina; Região do Caribe.

ABSTRACT

Objective: To quantitatively synthesize the published peer reviewed literature, presenting a pooled estimate of adherence to antiretroviral treatment (ART) of people living with HIV (PLHIV) in Latin America and Caribbean (LAC); to qualitatively synthetize the methods used to measure adherence and describe the factors associated with poor adherence among the selected studies.

Methods: We electronically searched published studies up to July 2016 on the PubMed, Web of Science and Virtual Health Library (Latin America and the Caribbean Regional Portal); considering the following databases: MEDLINE, LILACS, PAHO and IBECS. Two independent reviewers selected and extracted data on treatment adherence and study characteristics. Pooled estimate of adherence was performed using a random-effects model. Risk of bias in individual studies was assessed by two investigators using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS).

Findings: The meta-analysis included 53 studies published between 2005 and 2016, which analyzed 22 603 PLHIV in 25 LAC countries. Overall adherence in LAC was 70% (95% CI: 63-76; I^2 = 98%), similar to levels identified by studies conducted in developing regions. Subgroup analysis showed that adherence proportion was higher in the shortest adherence recall time frame used, and in countries with lower income level, Gross National Income (GNI) per capita and Human Development Index (HDI). Individual self-report was the most used method. Studies reported diverse adherence barriers, such as alcohol and substance misuse, depression, unemployment and pill burden.

Conclusion: Our study suggests that adherence to ART in LAC may be below the sufficient levels required for a successful long-term viral load suppression.

Keywords: Anti-HIV Agents; Antiretroviral Therapy, Highly Active; Medication Adherence, Developing Countries; Latin America; Caribbean Region.

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LISTA DE ABREVIATURAS E SIGLAS

ACTG	*Aids Clinical Trials Group*
AIDS	*Acquired Immunodeficiency Syndrome;* Síndrome da Imunodeficiência Adquirida
AOR	*Adjusted odds ratio;* Razão de chances ajustada
ARH	*Adjusted relative hazard;* Razão de riscos ajustada
ARR	*Adjusted relative risk;* Risco relativo ajustado
ART/TAR	*Antiretroviral Therapy;* Terapia antirretroviral
ARV	*Antiretrovirals;* Antirretrovirais
BVS	Biblioteca Virtual em Saúde
CAT-VIH	*Cuestionario de adherencia al tratamiento para el VIH/SIDA*
CD4	*CD4 + T cells;* Linfócitos T CD4+
CEAT-VIH	*Cuestionario para la Evaluación de la Adhesión al Tratamiento Antirretroviral*
GNI	*Gross National Income*
HAART	*Highly Active Antiretroviral Therapy;* Terapia antirretroviral de alta potência
HDI/IDH	*Human Development Index;* Índice de Desenvolvimento Humano
HIV	*Human Immunodeficiency Virus;* Vírus da Imunodeficiência Humana
IDU/UDI	*Injection drug use;* Uso de drogas injetáveis
LAC/ALC	*Latin America and Caribbean;* América Latina e Caribe
MEMS	*Medication Event Monitoring System*
n	Número amostral de participantes
ONU	Organização das Nações Unidas
PLHIV/PVHIV	*People living with HIV;* Pessoas que vivem com o HIV
PMAQ	*Patient Medication Adherence Questionnaire*
PRISMA	*Preferred reporting items for systematic reviews*
RoBANS	*Risk of Bias Assessment tool for Non-randomized Studies;* Avaliação de Risco de Viés para Estudos Não-Aleatórios
SMAQ	*Simplified Medication Adherence Questionnaire*
SR	*Self-report;* Autorrelato
UNAIDS	*United Nations Programme on HIV/AIDS;* Programa das Nações Unidas em HIV/AIDS
VPAD-24	*Variables psicológicas y comportamientos de adhesión*
WHOQOL-HIV	*World Health Organization's Quality of Life instrument (WHOQOL) module for HIV*

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1 INTRODUÇÃO

A partir de 1996, a terapia antirretroviral de alta potência (*Highly Active Antiretroviral Therapy*, HAART) se tornou padrão de tratamento da infecção pelo HIV. A HAART se baseia na combinação de três ou mais antirretrovirais (ARV), cujo objetivo principal é reduzir e manter a carga viral plasmática do HIV em níveis indetectáveis. A HAART revolucionou o tratamento de pessoas que vivem com o HIV (PVHIV) ao diminuir dramaticamente sua morbidade e mortalidade (PALELLA *et al*., 1998; MURPHY *et al*., 2001), conferindo à infecção pelo HIV a condição de doença crônica. Após duas décadas de HAART, temos esquemas menos tóxicos, mais eficazes, e de maior comodidade posológica, como é o caso dos comprimidos em dose fixa combinada. Mas apesar dos avanços no tratamento, a adesão à terapia antirretroviral (TAR) continua sendo um grande desafio no enfrentamento da epidemia do HIV/AIDS.

A adesão à TAR é considerada forte preditora da progressão para a AIDS (BANGSBERG, *et al*., 2001). Ótimos níveis de adesão à TAR permitem alcançar a recuperação imunológica (elevar o número de linfócitos T CD4+) e manter a carga viral do HIV indetectável (em geral < 50 cópias/mL) (PATERSON *et al*., 2000). O baixo apoio social, a depressão, o consumo de bebidas alcoólicas, o uso de drogas, os efeitos colaterais, a falta de aconselhamento e fatores socioeconômicos têm sido preditivos de baixa adesão à TAR em diversos continentes (SHUBBER *et al*., 2016 e LANGEBEEK *et al.*, 2014). Uma baixa adesão pode levar à falha virológica (carga viral plasmática detectável após seis meses do início ou modificação da TAR, ou por detecção da carga viral nos indivíduos que a mantinham indetectável na vigência de tratamento); a um acúmulo de mutações de resistência aos antirretrovirais (diminuindo as opções de tratamento) e a uma elevação menos robusta e duradoura da contagem de linfócitos T CD4+; além de maior progressão da doença (BRASIL, 2013).

Ainda não está claro o nível ideal de adesão para se obter o benefício máximo da TAR. Muitos consideram ideal uma adesão mínima de 95%. A “regra dos 95%” teve sua origem no estudo realizado por Paterson *et al*. na fase inicial da HAART, utilizando esquemas mais complexos e menos potentes (PATERSON *et al*., 2000). Neste estudo, participantes que tomaram 95% ou mais das doses prescritas, apresentaram maior supressão viral, maior recuperação imunológica e menor número de hospitalizações do que participantes com adesão inferior a 95%.

Posteriormente, outros autores demonstraram que elevados níveis de supressão viral poderiam ser obtidos com adesão inferior a 95% em esquemas mais modernos (MAGGIOLO *et al*., 2005; BANGSBERG, 2006; SHUTER *et al*., 2007; KOBIN AND SHETH, 2011; VISWANATHAN *et al*., 2015). Segundo Bangsberg (2006:941):

> Mesmo que a supressão viral seja possível em moderados níveis de adesão, a probabilidade de alcançá-la e, mais importante ainda, a probabilidade de reduzir a progressão da doença e mortalidade, aumenta a cada incremento no nível de adesão.

A proporção agregada de PVHIV em níveis adequados de adesão à TAR já foi estimada em 62% no nível global (ORTEGO *et al*., 2011), e entre 55% e 77% na América do Norte, Espanha, Índia e em países do continente africano (MILLS *et al*., 2006; ORTEGO, *et al*., 2011; MHASKAR *et al*., 2013). A proporção estimada de PVHIV na ALC em ótimos níveis de adesão ainda não foi estimada em uma metanálise.

O monitoramento dos níveis de adesão é recomendado pelas principais organizações de saúde do mundo. Os métodos mais utilizados para monitorar a adesão à TAR são autorrelato mediante entrevista, contagem de pílulas, registros em prontuários e de dispensação em farmácias, monitoramento eletrônico de medicamentos (*Medication Event Monitoring System* - MEMS), monitoramento de nível sérico terapêutico, registros diários de medicamentos, assim como métodos combinados. O autorrelato é o método mais amplamente utilizado para o monitoramento da adesão. Os questionários de autorrelato consideram perguntas sobre o número de doses tomadas ou perdidas, ou perguntas relativas à frequência com que ocorre a perda de doses, sempre considerando um período de tempo. O modelo de resposta é, em geral, no formato *Likert* (escala de geralmente cinco itens variando da resposta mais negativa até a mais positiva). Alguns exemplos de questionários de autorrelato específicos para a adesão à TAR são o CEAT-VIH (*Cuestionario para la Evaluación de la Adhesión al Tratamiento Antirretroviral*) o SMAQ (*Simplified Medication Adherence Questionnaire*) e os do grupo ACTG (*AIDS Clinical Trials Group*). Os instrumentos do ACTG, amplamente utilizados em todo o mundo, foram desenvolvidos com foco na adesão recente (últimos um a quatro dias) para minimizar o viés de memória (CHESNEY *et al*., 2000). Outras estratégias são utilizadas para aumentar a acurácia do resultado como por exemplo o uso da escala visual analógica (*Visual Analogue Scale, VAS*) como modelo de resposta. A VAS, originalmente criada para auxiliar na aferição da intensidade de dor,

é uma escala visual utilizada para mensurar características ou comportamentos que variam em um continuo geralmente representado de zero a 100. Quando utilizada em autorrelato para medir adesão, seus extremos se traduzem na perda total de doses (zero) até a adesão perfeita à medicação (100). Outro método desenvolvido para otimizar a medida do autorrelato através dos questionários do ACTG foi o índice de adesão de Reynolds e colaboradores (REYNOLDS *et al*., 2007), uma equação que utiliza as respostas de itens do questionário para calcular uma proporção de adesão. Todos os métodos de monitoramento da TAR, sejam eles subjetivos ou objetivos, apresentam suas vantagens e desvantagens. Os resultados podem ser superestimados ou subestimados, o que dificulta a acurácia da medição e a comparação entre estudos. Apesar dos desafios, o monitoramento da adesão é fundamental, pois possibilita a identificação dos usuários de TAR com baixa adesão, permitindo o planejamento de ações oportunas para cada caso. A detecção precoce da não adesão é extremamente importante, pois é capaz de prever a ocorrência de falha virológica (BISSON *et al*., 2008).

Na América Latina e Caribe (ALC) existem aproximadamente dois milhões de PVHIV e quase 1,1 milhões receberam TAR até o final de 2015 (UNAIDS, 2016). Apesar do aumento significativo na cobertura da TAR nos últimos anos, o número de óbitos não diminuiu tão drasticamente e o número de novas infecções permaneceu estático na ALC. No período de 2010 a 2015 houve um aumento de 23% na cobertura da TAR, e um declínio de 17% nos óbitos relacionadas à AIDS na ALC; no entanto, no mesmo período, o número de novas infecções manteve-se em 100.000 por ano (UNAIDS, 2017). A manutenção de níveis ótimos de adesão à TAR exerce um papel muito importante no enfrentamento da epidemia do HIV/AIDS, pois relaciona-se intimamente à supressão viral do HIV, diminuindo as taxas de transmissão e, consequentemente, o número de novas infecções (COHEN *et al.*, 2011). Conhecer melhor o comportamento de adesão à TAR, e os níveis de adesão atingidos na ALC é essencial para auxiliar governos e instituições locais a alcançar as metas estabelecidas especificamente para a região em declaração política da ONU de 2016 sobre a Eliminação da AIDS até 2030, que são: reduzir o número de novas infecções de 100.000 para 40.000 e aumentar o número de pessoas em TAR de 1,1 para 1,6 milhões de até 2020 (NAÇÕES UNIDAS, 2016).

1.1 Objetivos

O objetivo geral deste trabalho foi sintetizar a literatura publicada em revistas indexadas, apresentando uma estimativa da proporção agregada de pessoas vivendo com HIV na América Latina e Caribe em nível ótimo de adesão.

Os objetivos específicos foram sintetizar qualitativamente os métodos de monitoramento da adesão, e descrever os fatores associados à baixa adesão entre os estudos selecionados.

1.2 Estrutura da dissertação

Nesta dissertação os capítulos de revisão da literatura, metodologia, resultados e discussão estão apresentados a seguir em forma de manuscrito, em língua inglesa, formatado de acordo com os requisitos do periódico *Bulletin of the World Health Organization* para o qual será submetido para publicação.

2 ARTIGO

Adherence to Antiretroviral Therapy for HIV/AIDS in Latin America and the Caribbean: Systematic Review and Meta-Analysis

AUTHORS: Jessica de Mattos Costa, Thiago Silva Torres, Lara Esteves Coelho e Paula Mendes Luz.

2.1 Abstract

Objective: To quantitatively synthesize the published peer reviewed literature, presenting a pooled estimate of adherence to antiretroviral treatment (ART) of people living with HIV (PLHIV) in Latina America and Caribbean (LAC); to qualitatively synthetize the methods used to measure adherence and describe the factors associated with poor adherence among the selected studies.

Methods: We electronically searched published studies up to July 2016 on the PubMed, Web of Science and Virtual Health Library (LAC Regional Portal); considering the following databases: MEDLINE, LILACS, PAHO and IBECS. Two independent reviewers selected and extracted data on treatment adherence and study characteristics. Pooled estimate of adherence was performed using a random-effects model. Risk of bias in individual studies was assessed by two investigators using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS).

Findings: The meta-analysis included 53 studies published between 2005 and 2016, which analyzed 22 603 PLHIV in 25 LAC countries. Overall adherence in LAC was 70% (95% CI: 63-76; I^2 = 98%), similar to levels identified by studies conducted in developing regions. Subgroup analysis showed that adherence proportion was higher in the shortest adherence recall time frame used, and in countries with lower income level, Gross National Income (GNI) per capita and Human Development Index (HDI). Individual self-report was the most used method. Studies reported diverse adherence barriers, such as alcohol and substance misuse, depression, unemployment and pill burden.

Conclusion: Our study suggests that adherence to ART in LAC may be below the sufficient levels required for a successful long-term viral load suppression.

2.2 Introduction

Highly active antiretroviral therapy (HAART) revolutionized the treatment of people living with HIV (PLHIV) by dramatically decreasing their morbidity and mortality (1). In Latin America and the Caribbean (LAC) there are 2.0 million PLHIV and almost 1.1 million people (55%) were on antiretroviral therapy (ART) by the end of 2015. (2) Despite significant increases in ART coverage over the last years, the number of deaths has not dramatically decreased. From 2010 to 2015 there was a 23% increase in ART coverage and 17% decline in AIDS-related deaths in LAC. Most significantly, the number of new infections remained stable at about 100 000 per year in the region (3).

The Joint United Nations Programme on HIV/AIDS (UNAIDS) established the Fast-Track strategy to end the AIDS epidemic by 2030. (4) The first goal is the 90-90-90 target: by 2020, 90% of all people living with HIV will know their HIV status, 90% of people who know their status receiving treatment, and 90% of people on HIV treatment having a suppressed viral load so their immune system remains strong and they are no longer infectious. Other Fast-Track goals include: reducing new HIV infections globally to fewer than 500 000, reducing AIDS-related deaths to fewer than 500 000, and eliminating HIV-related stigma and discrimination by 2020. Specific goals for LAC, established by the Political Declaration on Ending AIDS by 2030 (5), include reducing the number of new infections in LAC from 100 000 to 40 000 and increasing the number of PLH on ART from 1.1 to 1.6 million people by 2020. Achievement of these goals will be challenging, requiring continued efforts from governments and international agencies.

AIDS epidemic cannot be ended without containing the new infections, and adherence to ART plays an important role in this process. The level of adherence to ART is closely related with suppression of the HIV viral load in plasma (6,7), decreasing HIV transmission rates (8). The optimal adherence level to achieve viral suppression is unclear, though the 95% threshold established by Paterson et al has largely been used as a goal (6). More recently, other authors demonstrated that high levels of viral suppression could be obtained with adherence below 95% in newer HAART regimens (9–13).

While many individuals on ART are able to maintain good adherence levels with consequential viral suppression, recovery of CD4+ T cell count and better clinical outcomes;

others, for multiple reasons, cannot achieve appropriate ART adherence levels. Monitoring patient's ART adherence is a challenging but critical way of identifying those with poor adherence.

Measures of adherence include individual self-report, pharmacy records, pill counts, electronic measurement devices, therapeutic drug concentrations and clinical outcomes. The easiest and therefore most frequently used method is patient self-report. Self-report questions consider the number or frequency of doses missed/taken, or simply asks individuals to rate their adherence level, always considering a specific time period. Questionnaires frequently use a Likert-type scale as the response format (often five-point ordered response ranging from the most positive to the most negative response to a statement). Although individual self-report can be inexpensive, easy to administer, and accurately identify medication-taking behavior, they may also overestimate adherence due to social desirability (i.e. respondents answer questions in a way that will be viewed favorably by clinicians) and memory biases.

The pooled proportion of people reporting adequate levels of ART adherence varies depending on the region where the study is conducted. It has been estimated by Ortego *et al* (14) as 62% (95% CI: 0.59-0.66; I^2 = 98.2%) worldwide, and by taking into account country's Human Development Index (HDI) values, they found that in low HDI countries the average proportion of adherence was higher than in high HDI countries. Mills and collaborators found a pooled estimate of 55% (95% CI: 0.49-0.62; I^2 = 98.6%) in North America and 77% (95% CI: 0.68-0.85; I^2 = 98.4%) in Africa. (15) In a meta-analysis by Uthman and collaborators (16) the proportion of PLHIV who achieved good adherence also tended to be higher in lower income countries (pooled rate = 86%; 95% CI: 0.62-0.96; I^2 = 98.1%) than middle (pooled rate = 74.4%; 95% CI: 0.63-0.83; I^2 = 96.9%) and high income countries (pooled rate = 67.5%; 95% CI: 0.62-0.73; I^2 = 97.8%). The estimated proportion of PLHIV in LAC with optimal adherence has not yet been reported in a meta-analysis.

In this meta-analysis, we synthesize the published peer reviewed literature, presenting a pooled estimate of adherence to ART of PLHIV in LAC. We also qualitatively synthetize the methods used to monitor adherence and describe the factors associated with poor adherence among the selected studies. Greater knowledge of ART adherence levels of PLH in LAC should help Governments and regional institutions to accomplish the goal of ending AIDS by 2030.

2.3 Methods

This systematic review and meta-analysis has been reported according to the *Preferred reporting items for systematic reviews and meta-Analyses* (PRISMA) *Statement* (17).

2.3.1 Protocol and registration

Key information about the design and conduct of this systematic review and meta-analysis are recorded at the international database of prospectively registered systematic reviews in health and social care (PROSPERO 2017:CRD42017055963) (18).

2.3.2 Eligibility criteria

Studies of any design were included if they met all the following criteria: (i) the study involved people living with HIV/AIDS in Latin America and the Caribbean; (ii) participants were receiving antiretroviral therapy; (iii) and treatment adherence was quantified based on a proportion of the population reaching a pre-determined adherence threshold. Studies were excluded if they included pregnant women, alternative forms of treatment (for example, due to some specific co-infection), or if antiretrovirals were being used for post or pre-exposure prophylaxis. Similarly, we excluded studies focusing on children or adolescents or specific populations (for example, only individuals previously found to have low adherence, homeless populations, among others). Studies were not excluded if it included adults and also participants less than 18 years of age, when adherence data was stratified by age (and in this case, data from the age categories <18 years were not considered in the present analysis). Articles published before 2005 were excluded to avoid studies in the pre-HAART era. Also, grey literature was not considered in this review.

2.3.3 Information sources

Articles were identified through searches conducted on 14 July 2016 on PubMed, Web of Science and Virtual Health Library (Latin America and the Caribbean Regional Portal)

considering the following databases: MEDLINE, LILACS, PAHO and IBECS. The search combined terms derived from four domains: (a) adherence; (b) HIV; (c) antiretroviral (d) countries of Latin America and the Caribbean. Citations were inserted into the study database when the four domains were jointly present in the title, abstract, MeSH terms or keywords. No limits were applied for language or publication date in the search.

2.3.4 Search strategy

The following search strategy was used in Web of Science database:

TS = (adherence OR nonadherence OR non-adherence) AND TS = (HIV OR AIDS OR PLHIV) AND TS = (Antiretroviral OR Antiretrovirals OR HAART OR ART) AND TS = ("Latin America" OR Latinoamerica OR Latin* OR "Central America" OR Centroamerica OR "Meso america" OR "Middle America" OR mesoamerica OR "South America" OR Sudamerica OR "America del sur" OR Caribbean OR Caribe OR Argentina OR Argentin* OR Bolivia* OR Brazil* OR Brasil* OR Colombia* OR Chile* OR Ecuador* OR Guiana OR Guyana OR Guayana OR Paraguay* OR Peru* OR Suriname OR Surinam* OR Uruguay* OR Venezuela OR Venez* OR Belize* OR "Costa Rica" OR "Costa Ric*" OR "El Salvador" OR Guatemala OR Guatemal* OR Honduras OR Hondur* OR Panama OR Panam* OR Mexico OR Mexic* OR Cuba* OR "Dominican Republic" OR "Republica Dominicana" OR Dominic* OR Haiti* OR Jamaica OR Jamaic*).

Strategies used in Virtual Health Library (LAC portal) and PubMed are available from the corresponding author on request. A reference manager (Zotero) was used to collect and organize search results and for duplicate removal.

2.3.5 Study selection

Two investigators (JMC, TST) reviewed all abstracts and full-text articles independently, according to the eligibility criteria in review protocol. Discrepancies were adjudicated by an independent third investigator (PML).

2.3.6 Data collection process

Data extraction was performed independently by two investigators (JMC, TST) using a predefined extraction form. Each paper was coded for publication characteristics (authors, publication year, full title, journal and language), study characteristics (the years when data were collected, the country where the study was performed, the study design [randomized controlled trial {RCT}, non-RCT longitudinal study or cross-sectional], the sample size, recruitment setting and number of study centers), participants characteristics (age, sex, race/ethnicity, time in use of ART, ART regimen, HIV-1 viral load and CD4 count), adherence monitoring characteristics (method for adherence measurement, cut-off of optimal adherence, proportion of adherents, time frame used to measure adherence), and the factors significantly associated with adherence ($p < 0.05$) on multivariate modeling. Discrepancies in extracted data were adjudicated by an independent third investigator (PML).

2.3.7 Study definitions

Adherence was estimated for each study by dividing the number of individuals with optimal adherence by the number of individuals evaluated. This implies that our overall pooled adherence was based on the adherence threshold adopted in each study. When a study examined the effect of an intervention on ART adherence, only the adherence data at the baseline was considered. In case there was no baseline assessment, only the first adherence assessment of the control group was extracted and analyzed. As adopted in prior studies (19,20) when more than one adherence measurement was reported, the most objective method was chosen for the analysis (e.g., MEMS > pill count > pharmacy refill > self-reported adherence in the past week > self-reported adherence in the past month). When an optimal adherence threshold (e.g., ≥ 80 or ≥ 95%) was not defined in the study and adherence was categorized in levels, the highest adherence category was considered.

For subgroup analysis, adherence recall time frame was categorized in four periods: 3-4 days, 7 days, 30 days and 90 days. Location/country was classified by geographical area and categorized as: Brazil, South America (Chile, Colombia, Peru), Central America and Caribbean (Cuba, Dominican Republic, Guatemala, Haiti, Jamaica), North America (Puerto Rico and

Mexico) and multi-region (included countries from more than one region). Time period when study was conducted was categorized as ≤ 2005, 2006-2010 and ≥ 2011. Study design was categorized as cross-sectional, longitudinal (non-RCT) and RCT. Income group was categorized by low/lower middle, upper middle, high and mix, following the World Bank definitions for 2017 (21). HDI ranking and the GNI per capita, were classified in two categories each (HDI: < 0.754 and ≥ 0.754; GNI per capita: < $ 14 145 and ≥ $ 14 145). HDI and GNI per capita data were extracted from the Human Development Reports of the United Nations Development Programme (22). When a study involved multiple countries, the lower HDI or GNI value was considered. Number of study sites was categorized as single-site, multi-site and online. Treatment experience was categorized as naïve, experienced and naïve and experienced. Instrument used to measure adherence were categorized as self-report, MEMS, self-report+withdrawal and self-report+pill count. Adherence threshold was categorized as <94%, 95%, 100% and not reported. Finally, the presence of statistical models evaluating factors associated with adherence (YES/NO) was evaluated in subgroup analysis.

2.3.8 Risk of bias in individual studies

The quality of the included studies was assessed by two investigators (PML, LEC.) using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) (23). The risk of bias in a study was graded as low, high or unclear based on the following study features: selection of participants (selection bias), consideration of confounding variables (selection bias), measurement of exposure (detection bias), handling of incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias).

2.3.9 Data synthesis

Logit transformation of the proportions and their standard errors were calculated to achieve a normal distribution which is required for the pooling of data (24). Pooled adherence proportion was calculated using the DerSimonian-Laird method (25) assuming a random-effects model. Heterogeneity between studies was initially evaluated by visual inspection of forest-plots.

The proportion of true heterogeneity to total variance was calculated by the Higgins I^2 statistic (26).

2.3.10 Publication bias

Any type of review has its validity threatened by the publication bias. Although very often authors try to avoid this bias by obtaining data from unpublished trials, the inclusion of this data can itself introduce bias. The studies that can be located by authors may be an unrepresentative sample of all unpublished studies. Also, it has been shown that published trials tend to be larger and present an overall greater treatment effect than grey trials (27). Additionally, including grey literature in this meta-analysis could jeopardize the results due to the risk regarding lower methodological quality of unpublished studies when compared to published and peer-reviewed studies, particularly in an adherence meta-analysis, where there is a considerable heterogeneity in the way of each study quantifies adherence. Indeed, the following results will show that heterogeneity was very high which implies funnel plot asymmetry. These findings suggest publication bias assessment unnecessary (24).

2.3.11 Additional analyses

We conducted subgroup analyses and estimated the pooled adherence proportion according to adherence recall time frame, location/country, time period when study was conducted, study design, country's income level, HDI rank, GNI per capita, sites, treatment experience, instrument to measure adherence, adherence threshold, and presence of statistical models evaluating factors associated with adherence.

2.4 Results

2.4.1 Study Characteristics

The flow diagram of study selection is shown in Figure 1. Fifty-three studies, comprehending 22 603 participants in ART from 25 LAC countries, met eligibility criteria for the

systematic review (Table 1) (28–80). The median number of participants in ART per study was 201 [range: 13-3,343; interquartile range (IQR): 394-125]. The studies were conducted between 2000 and 2013 and published from 2005 to 2016 in three different languages (English: 39; Spanish: 9; Portuguese: 5). Studies were mostly conducted in countries with an upper middle income level.

Adherence was most commonly self-reported via structured interviews. Forty-nine studies (92.4%), enrolling 21 974 participants, provided a self-reported adherence proportion. Forty-seven studies (88.7%) used self-report instruments only and one used MEMS only. Five studies (9.4%) used a combination of patient self-report, MEMS, pill count and information about medication withdrawals. The following standardized instruments were used to measure self-reported adherence: the AIDS Clinical Trials Group (ACTG) adherence instrument (81); the CAT-VIH - *Cuestionario de adherencia al tratamiento para el VIH/SIDA* (82); the CEAT-VIH - *Cuestionario para la Evaluación de la Adhesión al Tratamiento Antirretroviral* (83); the Morisky, Green & Levine Medication Adherence Scale (84); the PMAQ - Patient Medication Adherence Questionnaire (85); the SMAQ - Simplified Medication Adherence Questionnaire (86) and the VPAD-24 - *Variables psicológicas y comportamientos de adhesión* (87). Twenty-five studies (47.2%) did not report the instrument used or the instrument was designed for the study or adapted from other studies.

Two studies combined two different adherence measures reporting the overall optimal adherence proportion: Teixeira *et al*. (2013)(53) (ACTG questionnaire and pill count) and Pacífico *et al*. (2015)(74) (SMAQ questionnaire or medication withdrawal). Balandrán *et al* (2013) (57), assessed adherence using the ACTG questionnaire (5 items) and the adherence index, but only the results for the ACTG questionnaire were considered in this meta-analysis. Though as a general rule we opted to use reported data from the most objective methods, a few exceptions were made. Campbell *et al*. (2010) (38) used both self-report (VAS) and pill count for measuring adherence. Although pill count was the most objective measure, the time frame information was not available, thus only data from the 7-day recall self-report measure (VAS) were considered in the analysis. In Souza *et al*. (2016) (77), only the self-reported adherence measure was considered because the adherence as measured from medication dispensing data addressed a period greater than 3 months (the whole study period).

Studies used different thresholds to define optimal adherence (range: ≥ 64% to > 100%). The most common definitions used for optimal adherence were higher than 95% and 100% of prescribed doses. Adherence recall time frames varied between the last three days and the last 90 days. Seventeen studies (32.1%) did not clearly report the time frame used.

Twenty-four out of 53 studies evaluated factors associated with adherence using adjusted statistical models. Statistically significant factors ($p < 0.05$) associated with adherence to ART found by these studies are presented in Table 3. Some factors positively associated with adherence to ART were: high social support (33,50), good relationship with the physician (40,69); satisfaction with the healthcare service (33,73); and use of a counselling service (39). Some factors negatively associated with adherence to ART were: alcohol use or alcohol use disorders (28,39,53,65,78); substance use (53,73,78,79); high pill burden (28,48,63); depression symptoms (62,63,72); unemployment or irregular employment (28,63); and high or detectable HIV viral load (63,72).

2.4.2. Risk of Bias

The results of the risk of bias assessment for each study included in the meta-analysis are shown in Figure 2. The risk of selection biases due to the inadequate selection of participants was high in 43 studies, low in three and unclear in seven. The risk of selection biases due to the inadequate confirmation and consideration of confounding variables during the design and analysis phases was low in 36 studies, but high in the remaining 17. The risk of performance biases caused by inadequate measurements of exposure was low in 50 studies, high in two and unclear in one. The risk of attrition biases caused by the inadequate handling of incomplete outcome data was low in 47 studies and high in the remaining six. The risk of selective reporting bias was low in all studies.

2.4.3. Meta-analysis

The overall pooled adherence was estimated in 70% (95% CI: 63-76; I^2 = 98%) (Figure 3). Results differed when we stratified studies by the four pre-defined time frames: last 3-4 days, last 7 days, last 30 days and last 90 days. The pooled estimate for the shortest period was

significantly higher and somewhat less heterogeneous (80%; 95% CI: 74-85; I^2 = 93%) than for the longest period (55%; 95% CI: 26-81; I^2 = 96%) (Figure 4). We also recalculated the pooled proportion according to the location/country, and in Brazil, where most of studies were conducted, the adherence estimate was 64% (95% CI: 54-73; I^2 = 98%) (Figure 5).

Results of the subgroup analysis are shown in Table 2. Studies conducted in low or lower middle income countries showed a higher pooled adherence (83%; 95% CI: 63-93; I^2 = 81%) than in middle income countries (70%; 95% CI: 62-77; I^2 = 98%). In countries with a lower HDI (< 0.754), pooled adherence was higher (75%; 95% CI:64-84; I^2 = 99%) than in countries with a higher HDI (66%; 95% CI: 57-74; I^2 = 98%). Similarly, in countries with a lower GNI per capita (< $ 14 145) the pooled adherence was higher (75%; 95% CI: 65-83; I^2 = 99%) than in countries with a higher GNI per capita (65%; 95% CI: 55-74; I^2 = 98%). Studies addressing only ART naïve participants had lower pooled adherence (56%; 95% CI: 33-78; I^2 = 75%) than those including treatment experienced participants (69%; 95% CI: 62-75; I^2 = 98%). The pooled proportion of adherence for studies using patient's self-report was 71% (95% CI: 64-77; I^2 = 99%), quite similar to the overall results as expected given that self-report was the most frequent tool used to measure adherence.

2.5 Discussion

This is the first systematic review and meta-analysis that estimates a pooled proportion of adherence to ART in LAC, uniting evidence from 53 studies, 22 603 participants, in 25 countries. Results suggest that overall, 70% (95% CI: 63-76) of PLHIV in LAC were adherent to ART and thus that adherence to ART in LAC may be below the sufficient levels required for successful viral load suppression. Mills *et al*. (2006) (15), in a meta-analysis of adherence to ART in sub-Saharan Africa (27 studies; 12 116 participants) and Mhaskar *et al*. (2013) in a meta-analysis of adherence to ART in India (8 studies; 1666 participants)(88), found similar estimates for other low/middle income regions (77%; 95% CI: 68–85; I^2 = 98.4% and 70%; 95% CI: 59–81, I^2 = 96.3%, respectively) than that found by our study. Pooled proportion of adherence has also been estimated by other researchers for North America (55%)(15); Spain (55%)(89); worldwide (62%)(14); and for high-risk subgroups living with HIV such as drug users (60%)(90), pregnant

women (73.5%)(91); female sex workers (76%) (92), adolescents (62%) (19), prisoners (54.6%) (93) and different high risk populations living with HIV in China (77.61%).

Our results show that, when assessing adherence, depending on the time-frame for recall, different results might be achieved. Our results point to higher adherence (80%) in the shortest time frame and lower adherence (55%) in the longer time-frame. These findings are consistent with the meta-analysis of adherence among HIV-positive drug users, conducted by Malta *et al*. (2010) (90), where the pooled estimate for the shortest period was higher (71%) than the pooled estimated for the intermediate period (54%). Moreover, and again, similarly to Malta et al (2010) (90), the shortest time frame also yielded a less heterogeneous estimate of adherence. Taken together, these findings suggest that a shorter time frame might yield to estimates that are less prone to recall bias and thus more accurate. However, these does not yet seem to be any consensus as to the time frame that best predicts adherence.

There were no significant differences in the pooled adherence among different optimal adherence thresholds (<94%, 95%, 100%), which was similar to the findings of Ortego *et al*. (2011) (14). In a recent meta-analysis conducted by Bezabhe *et al*. (2016)(20), there were no significant differences in the pooled odds ratios for virologic failure among different optimal adherence thresholds (≥ 98–100%, ≥ 95%, ≥ 80–90%) showing that irrespective of the cut-off point, optimal adherence to ART was associated with positive clinical outcomes.

The proportion of people who reported optimal adherence to ART varied according to the country's income level, HDI and GNI per capita. We found that in studies from lower income countries the pooled proportion of adherence was higher than in studies from middle-income countries. HDI and GNI per capita followed the same trend. Studies in countries with a lower HDI and GNI per capita had higher proportions of adherence than studies in countries with a higher HDI and GNI per capita. These findings are consistent with previous meta-analysis: Uthman *et al*. (2014) (16) that found that the proportion of PLHIV who achieved good adherence was significantly higher in lower-income countries (86%) compared to higher-income countries (67.5%; $p < 0.05$). These findings suggest that less developed regions can achieve the same level of adherence as more developed ones. However, Bezabhe *et al*. (2016) (20) when exploring the impact of adherence on virologic failure found that the pooled odds ratio for virologic suppression among those with optimal adherence compared to suboptimal adherence for countries with low HDI (0.50; 95% CI: 0.35–0.72) was lower than for countries with very high

HDI (0.23; 95% CI: 0.15–0.33). Suggesting that although adherence might be similar, the expected effect of adherence on virologic suppression is lower in low/middle income countries. A possible explanation might be the lack of consistent virologic monitoring (94) with patients adhering to non-suppressive treatment.

The accurate measurement of adherence is a challenge and currently there is no gold standard. Patient's self-reported adherence was the most common method for assessing adherence in this meta-analysis. Self-report questionnaires, which have a reasonable predictive power, are useful for resource-limited clinical settings. The ACTG Adherence Questionnaire was the most extensively instrument used. It is a 5-item self-report measure, but frequently, only the first item (4-day recall of how many doses have been missed) is used in clinical setting. The other four ACTG questionnaire items capture multiple dimensions of ART adherence behavior, because they also consider adherence to schedules, especial instructions and when any of the antiretrovirals (ARV) were missed. Followed by the ACTG questionnaire, the CEAT-VIH was the second most used self-report instrument. The CEAT-VIH is a short (20 items) multidimensional self-report instrument to measure adherence, available in six languages: English, European Spanish and Latin American Spanish, European Portuguese, Brazilian Portuguese, and Romanian. The total score obtained by the sum of all CEAT-VIH items (minimum 17 - maximum 89) identifies the rate of adherence and enable the classification of the respondent according to his degree of adherence: "strict adherence (good)" percentile $\geq$ 85, "insufficient (struggling)" percentile between 84 to 50, and "insufficient (noncompliance)" percentile lower than 49. Dimensions of the CEAT-VIH include treatment compliance (adherence in the last week; adherence since treatment started; adherence to time schedule; patient's level of commitment and names of ARV) and factors that affect treatment adherence (antecedents of noncompliance; doctor–patient relationship; patient's beliefs about medication; intensity of side effects; degree of information and knowledge about medication; degree of satisfaction with treatment; perceptions of health benefits since the start of treatment and the use of strategies to remember taking medication). Although the medication event monitoring system (MEMS) has been used as measure of choice to validate adherence measures such as patient's self-report or pharmacy database (medication withdrawal or refill data), the cost of this device substantially impairs their widespread use. Clinical outcomes, such as HIV viral load, is considered by some researchers as one of the best measures of a patient's adherence behavior, but

the use of clinical outcomes as a proxy of adherence can always be biased by the presence of any patient or disease-related factor. Each adherence measurement strategy has strengths and weaknesses. The best measurement strategy for clinical practice shall take in consideration the setting, the population, and most importantly have acceptable reliability and validity.

The assessment of the quality of the measurement of medication adherence in published studies was challenging. Many studies have not reported relevant methodological details about the assessment of adherence, making it difficult to judge the strength of their findings. To promote improvement in the quality of measurement of medication adherence in research Williams *et al*. (95) have proposed a set of best practices for conducting adherence measurement. For studies using self-report, for example, it is recommended the use of an instrument and method of administration that demonstrate both concurrent and predictive validity. When using a new instrument, it needs to be validated in a pilot test. When a scale is used to measure adherence, it needs to be culturally sensitive, worded clearly, and subjects needs to know how to respond to the scaling response options with little difficulty. In addition to their recommendations, and to improve also the reporting of adherence measurement, we suggest that researchers clearly identify the instrument used, whether it was validated for use in study population, when the assessment was carried out (date), the adherence recall time frame used, the adherence definition used (i.e., no. of pills taken/prescribed or instrument score) and the optimal adherence cut-offs or thresholds adopted. Accurate assessment of adherence behavior is essential for treatment planning while accurate reporting of adherence studies is essential for further advancement of the subject. A reliable measurement tool can help healthcare providers to adjust the medication, change recommendations or even change the approach to the patient.

Since the beginning of ART, PLHIV have been facing multiple barriers to adherence. Nonadherence to ART is frequently caused by them, which not only affects patient's health but also the health care system, increasing heath care costs. Identifying specific barriers for each patient and implementing appropriate interventions to overcome them is extremely necessary to improve adherence. The social support was one of the factors associated with adherence in this systematic review and meta-analysis. Social network and social influence, can provide a powerful approach for health behavior change (96). Alcohol use was associated with nonadherence to ART in many studies. This association is very common between PLHIV, where alcohol abuse can be higher than in general population, and may lead to medical and psychiatric complications, poor

adherence and poorer treatment outcomes (97). Additionally, alcohol use is associated with intravenous drug use and risk sexual behavior, major modes of HIV transmission (97). Unemployment was another barrier to nonadherence in LAC countries. This association exists globally, and was recently estimated with a pooled odds ratio of 1.27 (95% CI: 1.04–1.55) in a meta-analysis carried out by Nachega *et al*. (2015) (98). Reporting of traditional barriers to ART such as toxicity and pill burden has reduced over time since current ART regimens are more accessible, simpler and well tolerated. Consequently, the primary barriers to adherence have changed. In a recent meta-analysis conducted by Shubber *et al*. (2016) (99), individual barriers most frequently reported by patients included forgetting, being away from home, and a change to daily routine. Depression, alcohol/substance misuse, stigma, feeling sick, health service-related barriers (i.e., distance to clinic) and stock outs were less frequently reported. In this systematic review and meta-analysis studies reported many traditional barriers, substantially those related with alcohol and substance misuse.

One limitation of this systematic review and meta-analysis is the high heterogeneity among different studies. Rates varied significantly across studies, possibly due to different populations, different thresholds, different time frames and methods of measurement. Accordingly, random effects models were chosen as our analytical framework to better accommodate the heterogeneity since it assumes that each study was drawn from populations that differ from each other in ways that could impact on the proportion of adherents. Heterogeneity was not entirely explained by subgroup analysis and we did not perform a meta-regression, so our results must be interpreted with caution. Additionally, we were not able to evaluate possible relationships between adherence and different regimens and patient characteristics because this information was rarely available among the included studies. Most of the studies used patient's self-report, a subjective measure susceptible to bias, to assess adherence to ART. Another limitation is that most of the studies included in this meta-analysis used a cross-sectional design, making it difficult to determine causal relationships between level of adherence and other factors. Lastly, we did not include grey literature so we may have missed studies that were relevant to our research question during the literature search.

In conclusion, our study suggests that PLHIV in LAC can achieve comparable adherence levels to other populations of developing regions though it may be below the sufficient levels required for a successful long-term viral load suppression. We encourage further studies of

adherence to ART in LAC considering not only how many doses have been missed but also multidimensional aspects of adherence to identify involved barriers and facilitators. We also identified the need to improve quality in conducting and reporting studies that assess adherence to ART to produce more consistent evidence that can be used to guide police makers of governments and regional institutions to improve ART adherence in LAC.

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2.6 References

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Figure 1. Flow diagram of study selection for the meta-analysis of adherence to antiretroviral therapy for HIV/AIDS in Latin America and the Caribbean, 2005-2016.

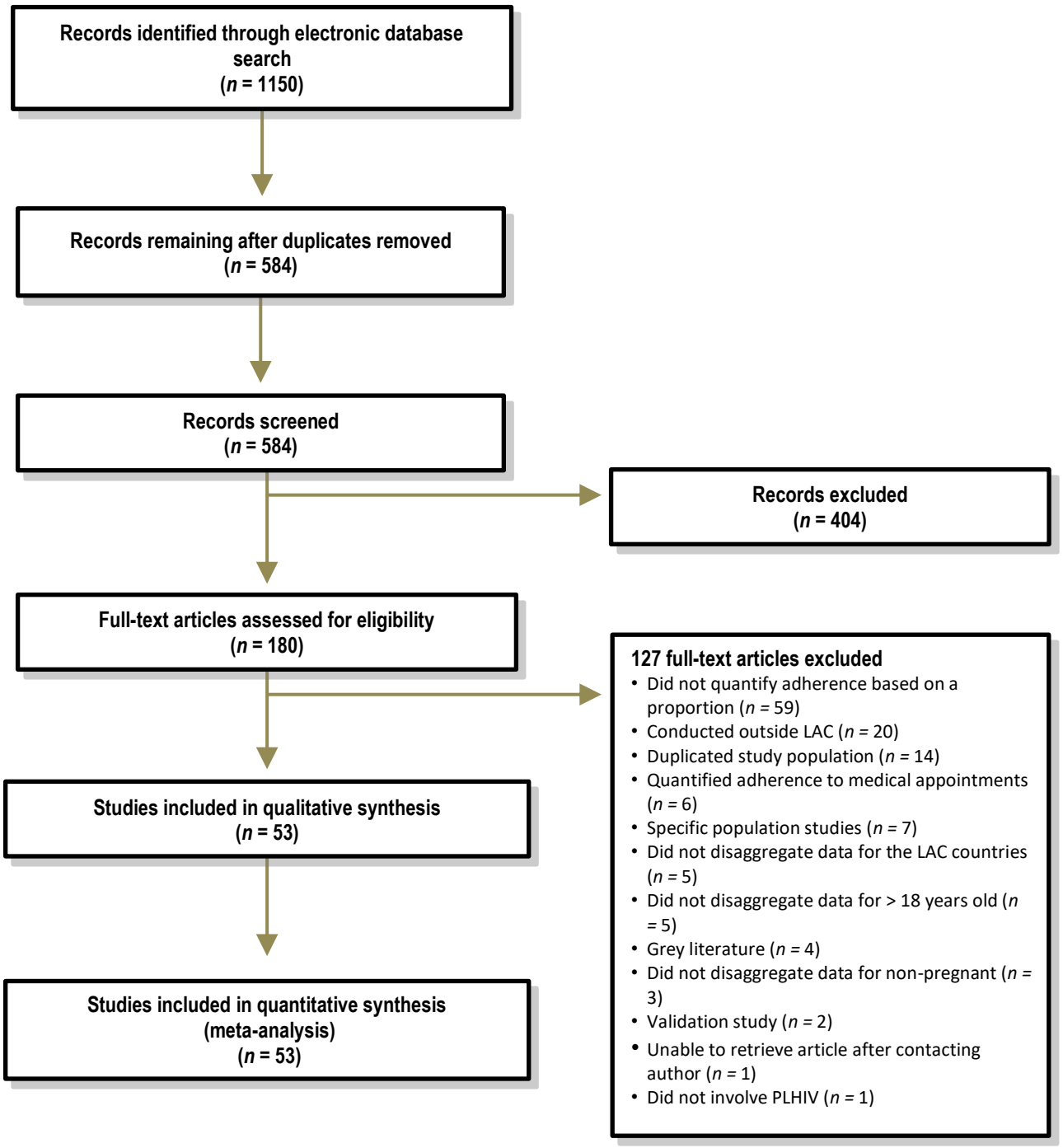


Figure 2. Risk of bias of studies included in the meta-analysis of adherence to antiretroviral therapy for HIV/AIDS in Latin America and the Caribbean, 2005-2016.

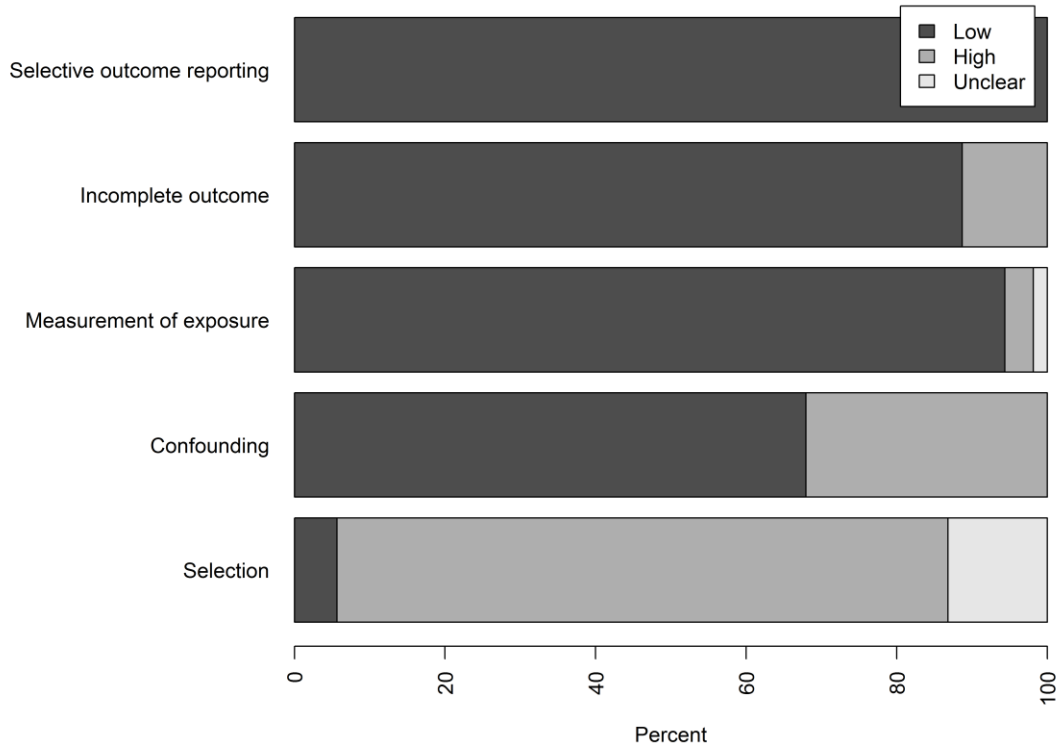


Figure 3. Pooled proportion of PLHIV adhering to antiretroviral therapy in Latin America and Caribbean, 2005-2016.

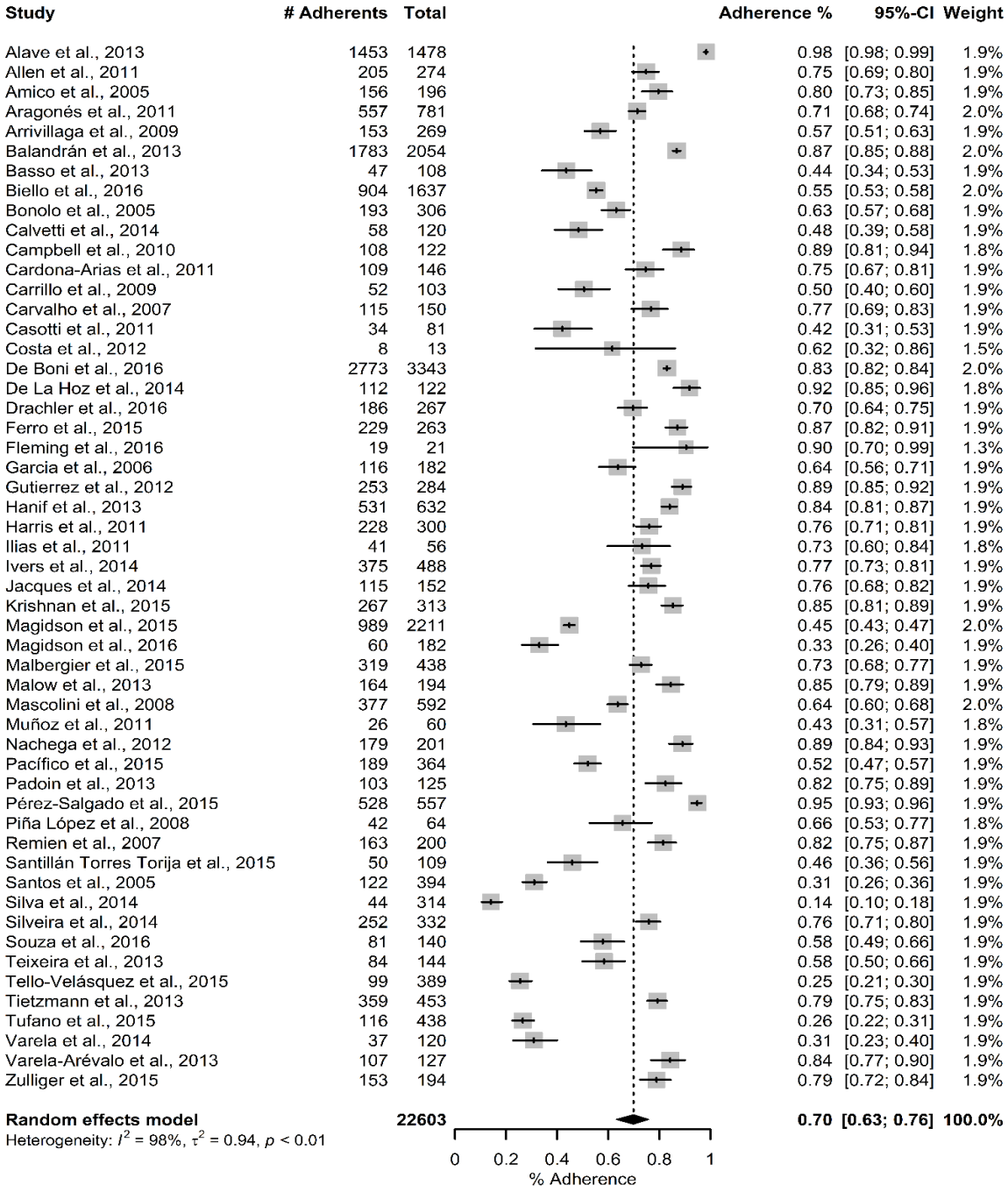
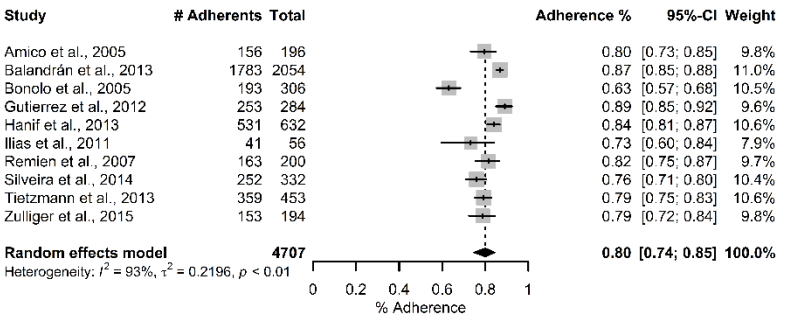
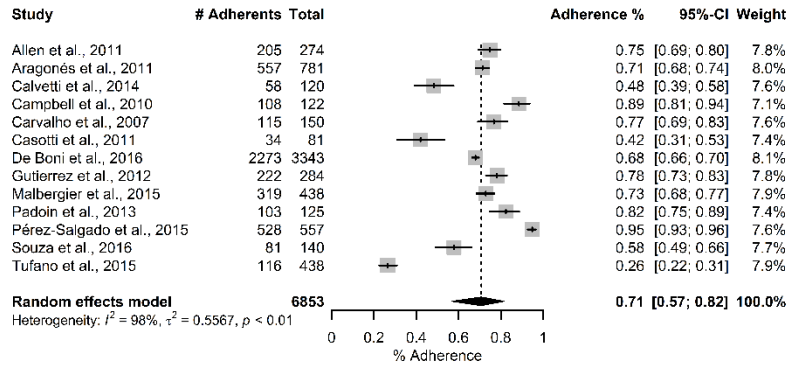


Figure 4. Pooled proportion of PLHIV adhering to ART in LAC by adherence recall time frame, 2005-2016. (a) 3-4 days; (b) 7 days; (c) 30 days, (d) 90 days.

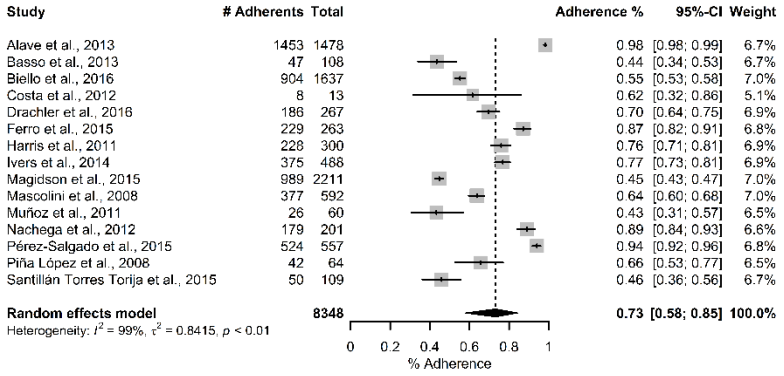
(a) 3-4 days



(b) 7 days



(c) 30 days



(d) 90 days

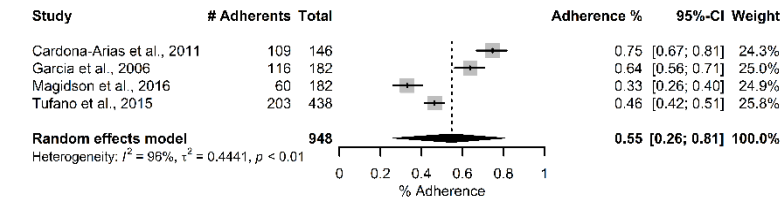


Figure 5. Pooled proportion of PLHIV adhering to ART in Brazil, 2005-2016.

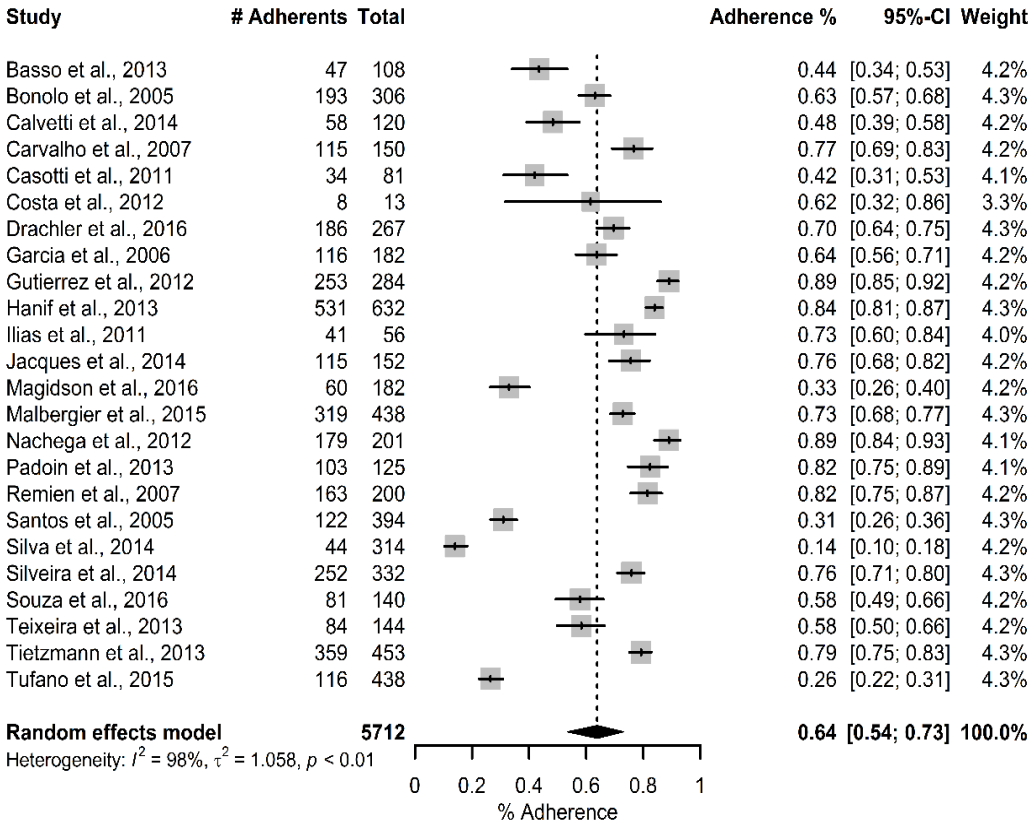


Table 1. Characteristics of studies included in the meta-analysis of adherence to antiretroviral therapy for HIV/AIDS in Latin America and the Caribbean, 2005-2016.

Source	LAC country	Study design	N in analysis	Adherence measure (instrument)	Optimal adherence threshold	Recall time frame(days)	Country's income group[a]	HDI[b]	GNI per capita[b]
Alave *et al*., 2013	Peru	Non-RCT longitudinal	1478	SR	> 95%	30	Upper middle	0.74	11,295
Allen *et al*., 2011	Antigua and Barbuda, Grenada, Trinidad and Tobago	Cross-sectional	274	SR	≥ 95%	7	Upper middle and high	0.754 - 0.786	11,502 - 28,049
Amico *et al*., 2005	Puerto Rico	Cross-sectional	196	SR (modified ACTG)	≥ 95%	3	High	Not available	Not available
Aragonés *et al*., 2011	Cuba	Cross-sectional	781	SR	≥ 95%	7	Upper middle	0.775	7,455
Arrivillaga *et al*., 2009	Colombia	Cross-sectional	269	SR	≥ 64%	Not reported	Upper middle	0.727	12,762
Balandrán *et al*., 2013	Mexico	Cross-sectional	2054	SR (ACTG)	≥ 95%	4	Upper middle	0.762	16,383
Basso *et al*., 2013	Brazil	RCT	108	MEMS	≥ 95%	30	Upper middle	0.754	14,145
Biello *et al*., 2016	17 countries[c]	Cross-sectional	1637	SR	100%	30	Lower middle, upper middle and high	0.625 - 0.847	4,466 - 21,665
Bonolo *et al*., 2005	Brazil	Non-RCT longitudinal	306	SR	≥ 95%	3	Upper middle	0.754	14,145
Calvetti *et al*., 2014	Brazil	Cross-sectional	120	SR (CEAT-VIH)	Not reported	Not reported	Upper middle	0.754	14,145
Campbell *et al*., 2010	Guatemala	Cross-sectional	122	SR (VAS) > Pill count	≥ 95%	7	Lower middle	0.64	7,063
Cardona-Arias *et al*., 2011	Colombia	Cross-sectional	146	SR (SMAQ)	Not reported	Not reported	Upper middle	0.727	12,762
Carrillo *et al*., 2009	Colombia	Cross-sectional	103	SR	Not reported	Not reported	Upper middle	0.727	12,762
Carvalho *et al*., 2007	Brazil	Non-RCT longitudinal	150	SR	≥ 95%	7	Upper middle	0.754	14,145
Casotti *et al*., 2011	Brazil	Cross-sectional	81	SR (CEAT-VIH)	≥ 85%	Not reported	Upper middle	0.754	14,145
Costa *et al*., 2012	Brazil	RCT	13	MEMS > Pill count > SR	> 95%	30	Upper middle	0.754	14,145

Source	LAC country	Study design	N in analysis	Adherence measure (instrument)	Optimal adherence threshold	Recall time frame(days)	Country's income group[a]	HDI[b]	GNI per capita[b]
De Boni *et al*., 2016	6 countries[d]	Cross-sectional	3343	SR	Not reported	7	Lower middle, upper middle and high	0.625 - 0.847	4,466 - 21,665
De La Hoz *et al*., 2014	Colombia	Cross-sectional	122	SR	≥ 80%	Not reported	Upper middle	0.727	12,762
Drachler *et al*., 2016	Brazil	Non-RCT longitudinal	267	SR	≥ 95%	30	Upper middle	0.754	14,145
Ferro *et al*., 2015	Peru	Cross-sectional	263	SR (VAS)	≥ 90%	30	Upper middle	0.74	11,295
Fleming *et al*., 2016	Dominican Republic	Cross-sectional	21	SR	100%	Not reported	Upper middle	0.722	12,756
Garcia *et al*., 2006	Brazil	Cross-sectional	182	SR (modified PMAQ)	> 95%	90	Upper middle	0.754	14,145
Gutierrez *et al*., 2012	Brazil	Cross-sectional	284	SR	100%	3, 7	Upper middle	0.754	14,145
Hanif *et al*., 2013	Brazil	Cross-sectional	632	SR (modified ACTG)	100%	4	Upper middle	0.754	14,145
Harris *et al*., 2011	Dominican Republic	Cross-sectional	300	SR (VAS)	≥ 95%	30	Upper middle	0.722	12,756
Ilias *et al*., 2011	Brazil	Cross-sectional	56	SR	≥ 80%	3	Upper middle	0.754	14,145
Ivers *et al*., 2014	Haiti	RCT	488	SR	100%	30	Low	0.493	1,657
Jacques *et al*., 2014	Brazil	Cross-sectional	152	SR (CEAT-VIH)	> 85%	Not reported	Upper middle	0.754	14,145
Krishnan *et al*., 2015	Peru	Cross-sectional	313	SR (VAS)	≥ 90%	Not reported	Upper middle	0.74	11,295
Magidson *et al*., 2015	17 countries[e]	Cross-sectional	2211	SR	100%	30	Lower middle, upper middle and high	0.625 - 0.847	4,466 - 21,665
Magidson *et al*., 2016	Brazil	Cross-sectional	182	SR	Not reported	90	Upper middle	0.754	14,145
Malbergier *et al*., 2015	Brazil	Cross-sectional	438	SR (SMAQ)	Not reported	7	Upper middle	0.754	14,145
Malow *et al*., 2013	Haiti	Cross-sectional	194	SR	Not reported	Not reported	Low	0.493	1,657
Mascolini *et al*., 2008	6 countries [f]	Cross-sectional	592	SR	Not reported	30	Upper middle and high	0.722 - 0.827	8,350 - 20,945
Muñoz *et al*., 2011	Peru	Non-RCT longitudinal	60	SR (ACTG)	≥ 95%	30	Upper middle	0.74	11,295
Nachega *et al*., 2012	Brazil	Cross-sectional	201	SR (ACTG)	100%	30	Upper middle	0.754	14,145
Pacífico *et al*., 2015	Peru	Cross-sectional	364	SR (SMAQ)+Withdrawal [g]	Not reported	Not reported	Upper middle	0.74	11,295
Padoin *et al*., 2013	Brazil	Cross-sectional	125	SR	100%	7	Upper middle	0.754	14,145
Pérez-Salgado *et al*., 2015	Mexico	Cross-sectional	557	SR	> 95%	7,30	Upper middle	0.762	16,383

Source	LAC country	Study design	N in analysis	Adherence measure (instrument)	Optimal adherence threshold	Recall time frame(days)	Country's income group[a]	HDI[b]	GNI per capita[b]
Piña López *et al*., 2008	Mexico	Cross-sectional	64	SR (VPAD-24)	100%	30	Upper middle	0.762	16,383
Remien *et al*., 2007	Brazil	Cross-sectional	200	SR (modified ACTG)	≥ 90%	3	Upper middle	0.754	14,145
Santillán Torres Torija *et al*., 2015	Mexico	Cross-sectional	109	SR (modified ACTG)	100%	30	Upper middle	0.762	16,383
Santos *et al*., 2005	Brazil	Cross-sectional	394	SR	Not reported	Not reported	Upper middle	0.754	14,145
Silva *et al*., 2014	Brazil	Cross-sectional	314	SR (CEAT-VIH)	≥ 85%	Not reported	Upper middle	0.754	14,145
Silveira *et al*., 2014	Brazil	RCT	332	SR	≥ 95%	3	Upper middle	0.754	14,145
Souza *et al*., 2016	Brazil	Cross-sectional	140	SR (CEAT-VIH) > Withdrawal	Not reported	7	Upper middle	0.754	14,145
Teixeira *et al*., 2013	Brazil	Non-RCT longitudinal	144	Pill count+SR (ACTG)[h]	≥ 95%	Not reported	Upper middle	0.754	14,145
Tello-Velásquez *et al*., 2015	Peru	Cross-sectional	389	SR (CEAT-VIH)	Not reported	Not reported	Upper middle	0.74	11,295
Tietzmann *et al*., 2013	Brazil	Cross-sectional	453	SR	≥ 95%	3	Upper middle	0.754	14,145
Tufano *et al*., 2015	Brazil	Cross-sectional	438	SR (SMAQ)	Not reported	7, 90	Upper middle	0.754	14,145
Varela *et al*., 2014	Chile	Cross-sectional	120	SR (Morisky-Green-Levine)	Not reported	Not reported	High	0.847	21,665
Varela-Arévalo *et al*., 2013	Colombia	Cross-sectional	127	SR (CAT-VIH)	> 90%	Not reported	Upper middle	0.727	12,762
Zulliger *et al*., 2015	Dominican Republic	Cross-sectional	194	SR (ACTG)	100%	4	Upper middle	0.722	12,756

Abbreviations: ACTG = Aids Clinical Trials Group ; CAT-VIH = *Cuestionario de adherencia al tratamiento para el VIH/SIDA* ; CEAT-VIH = *Cuestionario para la Evaluación de la Adhesión al Tratamiento Antirretroviral*; MEMS = medication event monitoring system ; PMAQ = Patient Medication Adherence Questionnaire; RCT = randomized clinical trials; SMAQ = Simplified Medication Adherence Questionnaire; SR = self-report ; VAS = visual analogue scale ;

[a] Study countries were categorized according to the income group, as defined by the World Bank for 2017 (21).

[b] Study countries were categorized according to the United Nations Human Development Index (HDI) ranking and the Gross National Income (GNI) per capita (based on purchasing power parity in constant 2011 international dollars), as defined by the United Nations Development Programme (22).

[c] Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay and Venezuela.

[d] Argentina, Brazil, Chile, Honduras, Mexico and Peru.

[e] Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay and Venezuela.

[f] Argentina, Brazil, Dominican Republic, Jamaica, Mexico and Puerto Rico.

[g] Used two methods to measure adherence, self-report or medication withdrawal, to calculate study proportion of participants in optimal adherence.

[h] Used two methods to measure adherence, self-report and pill count, to calculate study proportion of participants in optimal adherence.

Table 2. Subgroup analysis of studies included in the meta-analysis of adherence to antiretroviral therapy for HIV/AIDS in Latin America and the Caribbean, 2005-2016.

				Tests for Heterogeneity	
Analysis group	**No of Studies**	**Sample size**	**Pooled Adherence (95% CI)**	***P*-value (Q Statistic)**	**I^2 (%)**
Overall	53	22603	0.70 (0.64, 0.75)	< 0.01	98%
Time frame					
3-4 days	10	4707	0.80 (0.74, 0.85)	< 0.01	93%
7 days	13	6853	0.71 (0.57, 0.82)	< 0.01	98%
30 days	15	8348	0.73 (0.58, 0.85)	< 0.01	99%
90 days	4	948	0.55 (0.26, 0.81)	< 0.01	96%
Location/country					
Brazil	24	5712	0.64 (0.54, 0.73)	< 0.01	98%
SA (Chile, Colombia, Peru)	12	3754	0.71 (0.49, 0.87)	< 0.01	99%
CA/Carribbean (Cuba, DR, Guatemala, Haiti, Jamaica)	7	2100	0.79 (0.73, 0.85)	< 0.01	80%
NA (Mexico, Puerto Rico)	5	2980	0.79 (0.47, 0.94)	< 0.01	98%
Multi-site	5	8057	0.66 (0.44, 0.82)	< 0.01	100%
Study period					
≤2005	5	1396	0.68 (0.39, 0.87)	< 0.01	98%
2006-2010	24	7328	0.71 (0.60, 0.79)	< 0.01	97%
≥ 2011	12	10025	0.66 (0.45, 0.82)	< 0.01	99%
Study design					
Cross-sectional	43	19257	0.69 (0.62, 0.76)	< 0.01	99%
Longitudinal	6	2405	0.75 (0.38, 0.94)	< 0.01	98%
RCT	4	941	0.66 (0.39, 0.86)	< 0.01	94%
Country's income level[a]					
Low/Lower middle	3	804	0.83 (0.63, 0.93)	< 0.01	81%
Upper middle	43	13426	0.70 (0.62, 0.77)	< 0.01	98%
High	2[c]				
Mix	5	8057	0.66 (0.44, 0.82)	< 0.01	100%
HDI[b]					
< 0.754	21	12736	0.75 (0.64, 0.84)	< 0.01	99%
≥ 0.754	31	9671	0.66 (0.57, 0.74)	< 0.01	98%
GNI per capita[b]					
< 14145	23	13791	0.75 (0.65, 0.83)	< 0.01	99%
≥ 14145	29	8616	0.65 (0.55, 0.74)	< 0.01	98%
Sites					
Single	27	6579	0.65 (0.52, 0.76)	< 0.01	98%
Multi	23	11585	0.77 (0.70, 0.82)	< 0.01	96%
Online	3	4440	0.55 (0.31, 0.76)	< 0.01	98%

Treatment experience					
Naïve	3	510	0.56 (0.33, 0.78)	< 0.01	75%
Experienced	48	20594	0.69 (0.62, 0.75)	< 0.01	98%
Naïve and experienced	2[c]				
Instrument to measure adherence					
Self-report	49	21974	0.71 (0.64, 0.77)	0.02	99%
MEMS	2[c]				
Self-report+Withdrawal[d]	1[c]				
Self-report+Pill Count[e]	1[c]				
Adherence threshold					
< 94%	10	1897	0.72 (0.51, 0.86)	< 0.01	98%
95%	18	7777	0.77 (0.66, 0.85)	< 0.01	97%
100%	11	5966	0.75 (0.62, 0.84)	< 0.01	98%
Not reported	14	6963	0.53 (0.40, 0.66)	< 0.01	99%
Statistical models evaluating factors associated with adherence					
Yes	24	11425	0.70 (0.60, 0.78)	< 0.01	98%
No	29	11178	0.70 (0.60, 0.79)	< 0.01	99%

Abbreviations: CA = Central America countries; CI = confidence interval; DR = Dominican Republic; GNI = Gross National Income; HDI = United Nations human development index; MEMS = medication event monitoring system; NA = not applicable to SA or CA; RCT = randomized clinical trials; SA = South American countries.

[a] Study countries were categorized according to the income group, as defined by the World Bank for 2017 (21).

[b] Study countries were categorized according to the United Nations Human Development Index (HDI) ranking and the Gross National Income (GNI) per capita (based on purchasing power parity in constant 2011 international dollars), as defined by the United Nations Development Programme (22). When a study involved multiple countries, the lower HDI or GNI value was considered.

[c] When the number of studies in each group was ≤ 2, meta-analysis was not performed.

[d] Used two methods to measure adherence, self-report or medication withdrawal, to calculate study proportion of participants in optimal adherence.

[e] Used two methods to measure adherence, self-report and pill count, to calculate study proportion of participants in optimal adherence.

Table 3. Factors associated with adherence to antiretroviral therapy for HIV/AIDS in Latin America and the Caribbean, for 24 studies with available data, 2005-2016.

Source	Factors associated with adherence
Allen *et al*., 2011	Use of a counseling service (AOR = 3.20; 95% CI: 1.55-6.61; $p = 0.002$) Revelation of HIV status without consent (AOR = 2.31; 95% CI: 1.13-4.74; $p = 0.023$) Alcohol consumption (AOR = 0.47; 95% CI: 0.23-0.96; $p = 0.039$) Side effects (AOR = 0.32; 95% CI: 0.15-0.68; $p = 0.003$)
Aragonés *et al*., 2011	Communication with the physician (AOR = 1.457; 95% CI: 1.010-2.103; $p = 0.044$) Change in treatment (AOR = 1.597; 95% CI: 1.083-2.358; $p = 0.018$) Memory (AOR = 3.175; 95% CI: 2.112-4.774; $p = 0.000$) Self-efficacy (AOR = 2.976; 95% CI: 1.999-4.433; $p = 0.000$) Commitment to treatment (AOR = 1.597; 95% CI: 1.093-2.334; $p = 0.016$) Confidence in treatment (AOR = 1.817; 95% CI: 1.245-2.650; $p = 0.002$)
Arrivillaga *et al*., 2009	Membership in the subsidized national health care plan[a] or being uninsured (AOR = 3.478; 95% CI: 1.957–6.181; $p < 0.0001$) when compared to the contributive plan.
Biello *et al*., 2016	Age (AOR = 1.02; 95% CI: 1.00-1.03; $p = 0.04$) Hard drug use during sex (AOR = 0.72; 95% CI: 0.53-0.96; $p = 0.03$)
Bonolo *et al*., 2005	(Nonadherence) Unemployment (ARH = 2.17; 95% CI: 1.19–3.96; $p = 0.011$) Alcohol use (ARH = 2.27; 95% CI: 1.58–3.25); $p < 0.001$) Self-report of three or more adverse reactions (ARH = 1.64; 95% CI: 1.09–2.48); $p = 0.017$) Number of pills per day (ARH = 2.04; 95% CI: 1.11–3.76); $p = 0.02$) Switch in antiretroviral regimen (ARH = 2.72; 95% CI: 1.84–4.03); $p < 0.001$) Use of more than one health service (RH = 0.54; 95% CI: 0.36–0.80; $p = 0.002$) Longer time between HIV test and 1st prescription (ARH = 2.27; 95% CI: 1.52–3.40; $p < 0.001$)
Calvetti *et al*., 2014	Social class (middle) (AOR = 3.5250; 95% CI: 1.229-10.080; $p = 0.019$) Perceived HIV stage (symptomatic) (AOR = 0.346; 95% CI: 0.138-0.871; $p = 0.024$) WHOQOL-HIV bref[b] domain I/physical[c] (AOR = 1.276; 95% CI: 1.010-1.613; $p = 0.041$) WHOQOL-HIV bref[b] domain V/environment[c] (AOR = 1.415; 95% CI: 1.158-1.728; $p = 0.001$)
Carvalho *et al*., 2007	(Nonadherence) Lower educational level (AOR = 18.4 ; 95% CI: 2.9 - 118.8; $p = 0.002$) Profession (AOR = 0.2 ; 95% CI: 0.0 - 0.9 ; $p = 0.047$) Income (AOR = 1.0 ; 95% CI: 1.0 - 1.0 ; $p = 0.007$) High social support (AOR = 10.6 ; 95% CI: 1.4 - 79.1 ; $p = 0.022$) Satisfaction with the service at the pharmacy (AOR = 32.5 ; 95% CI: 4.6 - 227.9 ; $p = 0.000$) Healthcare reference center in *Plano Piloto* (an urban planned location vs. unplanned) (AOR = 0.2; 95% CI: 0.1-0.7; $p = 0.014$)
Casotti *et al*., 2011	Higher educational level (AOR = 1.40; 95% CI: 1.10-1.78; $p = 0.006$) longer duration of undetectable viral load (AOR = 1.03; 95% CI: 1.00-1.06; $p = 0.02$)

De Boni *et al*., 2016	(Nonadherence - missed doses) Substance use ($p < 0.001$): alcohol use compared to no substance use (AOR = 2.46; 95% CI: 1.99–3.05) illicit drug use compared to no substance use (AOR = 3.57; 95% CI: 2.02–6.30) using both alcohol and illicit drugs compared to no substance use (AOR = 4.98; 95% CI: 3.19–7.79) HIV transmission mode ($p < 0.001$): homosexual vs. heterosexual (AOR = 0.88; 95% CI: 0.67-1.16) IDU vs. heterosexual (AOR = 2.46; 95% CI: 1.04-5.83) others vs. heterosexual (AOR = 1.44; 95% CI: 1.05-1.98) Age (per 10 years increase) (AOR = 0.88; 95% CI: 0.80-0.98; $p = 0.02$) Study site (AOR = 1.87; 95% CI: 1.17–3.01 for IHSS/HE-Honduras vs. FH-Argentina AOR = 0.08; 95% CI: 0.04–0.16 for INCMNSZ-Mexico vs. FH-Argentina; $p < 0.001$)
Drachler *et al*., 2016	(Nonadherence) SEA-ART[d] score (per each unit increase) (AOR = 0.92; CI 95%: 0.90-0.95; $p = 0.002$)
Ferro *et al*., 2015	Having an alcohol use disorder with optimal adherence (AOR = 0.427; 95% CI: 0.187–0.976; $p = 0.044$) Having an alcohol use disorder with perfect adherence (AOR = 0.552; 95% CI: 0.327–0.930; $p = 0.026$)
Gutierrez *et al*., 2012	Having symptoms prior to ART ($p = 0.039$) Taking fewer ART pills ($p = 0.003$) Not missing medical appointments ($p < 0.0001$)
Hanif *et al*., 2013	Having one child (compared to 0 or ≥ 2) (AOR = 2.29; 95% CI: 1.33-3.94; $p = 0.003$) High social support (AOR = 2.85; 95% CI: 1.50-5.41; $p = 0.001$) High asset index (AOR = 2.47; 95% CI: 1.79-3.40; $p = 0.000$) Gender female (AOR = 0.58; 95% CI: 0.38-0.88; $p = 0.011$)
Pérez-Salgado *et al*., 2015	(Low adherence) Patient dissatisfaction about relationship with the physician (AOR = 1.90; 95% CI: 1.01-3.57); $p = 0.046$)
Piña López *et al*., 2008	The combination of intermediate levels of stress associated with tolerance to ambiguity and low levels of depression ($p = 0.027$)
Remien *et al*., 2007	(Nonadherence) Sexual orientation (heterosexual versus homosexual/bisexual) (AOR = 2.69; 95% CI: 1.08–6.66; $p < 0.05$) Difficulty to tailoring therapeutic regimen to daily routine (AOR = 2.56; 95% CI: 1.07–6.14; $p < 0.05$) Loss of appetite in the last month (AOR = 3.56; 95% CI: 1.31–9.62; $p < 0.05$)
Silveira *et al*., 2014	No regular employment (ARR = 0.91; 95% CI: 0.82–1.00; $p = 0.05$) Detectable plasma viral load (ARR = 0.83; 95% CI: 0.73–0.95); $p = 0.01$) Depressive symptoms (ARR = 0.99; 95% CI: 0.99–1.00); $p = 0.04$) Number of tablets daily (ARR = 0.96; 95% CI: 0.93–0.98); $p < 0.01$)
Teixeira *et al*., 2013	Intensity of alcohol use (AOR = 3.29; 95% CI: 1.83–5.92; $p < 0.001$) Use of alcohol and multiple substances (AOR = 5.99; 95% CI: 1.78–20.28; $p = 0.004$)
Tello-Velásquez *et al*., 2015	(Nonadherence) Moderate/severe poor quality of sleep (APR = 1.34; 95% CI: 1.17-1.54; $p = 0.001$)
Tietzmann *et al*., 2013	Gender male (APR = 1.37; 1.24-1.52; $p = 0.000$) Low and moderate clinical status (compared to severe) (APR = 1.18; CI 95%: 1.04-1.35; $p = 0.009$)

Tufano *et al*., 2015	Nonadherence in last 7 days: Age in years (AOR = 0.96; CI 95%: 0.93-0.98; $p < 0.01$) Hamilton Depression Rating Scale (AOR = 1.04; CI 95%: 1.01-1.07; $p < 0.01$) Viral load (AOR = 1.21; CI 95%: 1.03-1.42; $p < 0.05$) Nonadherence in last 90 days: Age in years (AOR = 1.02; CI 95%: 1.00-1.05; $p < 0.05$) Viral load (AOR = 1.21; CI 95%: 1.03-1.42; $p < 0.05$) Heterosexual HIV transmission mode (compared to homo/bisexual) (AOR = 0.52; CI 95%: 0.28-0.96; $p < 0.05$) Unknown HIV transmission mode (compared to homo/bisexual) (AOR = 0.10; CI 95%: 0.01-0.88; $p < 0.05$) CD4+ cell count (AOR = 0.99; CI 95%: 0.99-1.00; $p < 0.05$)
Varela *et al*., 2014	Nonadherence: Moderate-severe depressive symptoms [Exp(B) = 3.08; CI 95%: 1.08-8.80; $p = 0.023$]
Varela-Arévalo *et al*., 2013	Barriers to treatment (AOR = 7.9; CI 95%: 2.04-30.59; $p = 0.003$) Men with no family member with HIV (AOR = 0.10; CI 95%: 0.01-0.73; $p = 0.023$) Women with no family member with HIV (AOR = 0.05; CI 95%: 0.00-0.73; $p = 0.028$)
Zulliger *et al*., 2015	Nonadherence: 'Female sex worker'-related discrimination (AOR = 3.24; CI 95%: 1.28-8.20; $p \leq 0.05$) Use of any drug (AOR = 2.41; CI 95%: 1.09-5.34; $p \leq 0.01$) Worked in a 'Female sex worker' establishment (AOR = 2.35; CI 95%: 1.20-4.60; $p \leq 0.05$) Internalized stigma related to female sex work (AOR = 1.09; CI 95%: 1.02-1.16; $p \leq 0.05$) Positive perceptions of HIV providers (AOR = 0.91; CI 95%: 0.85-0.98; $p \leq 0.05$)

Abbreviations: AOR = adjusted odds ratio; ARR = adjusted relative risk; ARH = adjusted relative hazard; IDU = injection drug use.

[a] General System of Social Security in Health (*Sistema General de Seguridad Social en Salud*, SGSSS - Colombia).

[b] WHOQOL-HIV bref is a shorter version of the original instrument WHOQOL-HIV, a multi-dimensional instrument designed to assess the quality of life of people infected with human immunodeficiency virus (HIV).

[c] Domain I of WHOQOL-HIV bref includes physical pain, physical problem, energy and sleep quality; and domain V includes physical safety, housing, finance, care (access to quality health care and social services), information, leisure time, physical environment (pollution / noise / transit / climate) and transport.

[d] The scale of Self-efficacy Expectations of Adherence to Antiretroviral Treatment (SEA-ART) assesses patients' expectations of their own ability to follow the antiretroviral prescription in 21 high-risk situations for non-adherence to ART.

3 CONCLUSÕES

Esta revisão sistemática e metanálise foi capaz de estimar que a proporção agregada de pessoas vivendo com HIV na América Latina e Caribe em nível ótimo de adesão é de 70%, mostrando que a adesão à TAR na ALC pode estar abaixo dos níveis necessários para assegurar supressão a longo prazo da carga viral. A heterogeneidade entre os estudos foi além das diferenças entre métodos e períodos de avaliação, exigindo uma abordagem de análise que levasse em consideração tais diferenças. Parte da heterogeneidade entre os estudos pôde ser explicada pelo período de avaliação da adesão, onde foi observado que a maior proporção de aderentes se deu no menor período avaliado (3-4 dias), e a menor proporção de adesão, no maior período (90 dias). O grau de desenvolvimento de cada país também foi responsável por diferenças nos níveis de adesão. Os níveis de renda (baixa/média baixa versus média alta), o índice de desenvolvimento humano (IDH < 0,754 versus IDH ≥ 0,754), e a renda per capita anual (< $ 14.145 versus ≥ $ 14.145) foram inversamente proporcionais à adesão.

Os métodos de monitoramento da adesão foram diversos, mas houve predominância dos que se baseiam no autorrelato do indivíduo, o que pode ter influenciado a estimativa da proporção agregada, já que podem superestimar a adesão.

Os fatores intervenientes no processo de adesão foram multidimensionais. Apoio social, uso de serviços de aconselhamento, boa relação médico-paciente, satisfação com o serviço de saúde, lembrar de tomar o medicamento na hora correta, expectativa de auto eficácia do tratamento, elevado nível de escolaridade, menor número de comprimidos, maior renda foram fatores associados positivamente à adesão à TAR. Enquanto que, uso de álcool ou drogas, desemprego, mudança no tratamento, efeitos colaterais, uso de drogas durante o sexo, elevado número de comprimidos diários, maior tempo entre o diagnóstico e o início da TAR, baixo nível de escolaridade e depressão foram fatores associados negativamente à adesão à TAR nos estudos incluídos neste trabalho.

A qualidade do monitoramento e da maneira como este foi reportado no texto dos artigos variou significantemente entre os estudos. Informações essenciais em estudos de adesão como: método, instrumento, período monitorado e ano de condução do estudo, não foram descritas em alguns artigos.

4 RECOMENDAÇÕES

O objetivo principal do monitoramento da adesão à TAR é melhorar a assistência ao paciente a medida que aumentamos o nosso conhecimento acerca do comportamento de sua adesão. Dessa forma podemos estabelecer as bases que precisamos para elaborar intervenções efetivas e apropriadas para cada caso.

Alcançar esse objetivo quando não temos um padrão de referência bem estabelecido para mensurar a adesão é uma tarefa árdua, mas que vem se aprimorando ao passar dos anos. A tecnologia, a busca por qualidade dos resultados e o entendimento sobre a complexidade do processo de adesão, vêm contribuindo grandemente para essa empreitada.

Estudos futuros devem buscar utilizar instrumentos validados, minimizar fontes de confundimento e reportar com exatidão a metodologia utilizada, para produzir evidências mais acuradas, que possam servir de base não só para orientar a prática clínica, mas também para a criação de políticas públicas e ações promotoras da adesão.

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ANEXO

RoBANS (Risk of Bias Assessment tool for Non-randomized Studies)

Table. The developed and validated version of RoBANS

Domain	Description	Risk of bias
Selection of participants	Selection bias caused by inadequate selection of participants	□ Low □ High □ Unclear
Confounding variables	Selection bias caused by inadequate confirmation and consideration of confounding variable	□ Low □ High □ Unclear
Intervention (exposure) measurement	Performance bias caused by inadequate measurement of intervention (exposure)	□ Low □ High □ Unclear
Blinding of outcome assessment	Detection bias caused by inadequate blinding of outcome assessment	□ Low □ High □ Unclear
Incomplete outcome data	Attrition bias caused by inadequate handling of incomplete outcome data	□ Low □ High □ Unclear
Selective outcome reporting	Reporting bias caused by selective outcome reporting	□ Low □ High □ Unclear

APÊNDICE A

Preferred reporting items for systematic reviews: PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	6
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9-10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	30
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15, 31
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	35-37
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15, 32-34
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

APÊNDICE B

Estratégia de busca realizada em título ou abstract ou descritores em ciências da saúde no PubMed.

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APÊNDICE C

Estratégia de busca realizada em título ou resumo ou assunto na Biblioteca Virtual em Saúde.

((ti:(adesao OR adherence OR nonadherence OR non-adherence)) OR (ab:(adesao OR adherence OR nonadherence OR non-adherence)) OR (mh:(adesao OR adherence OR nonadherence OR non-adherence))) AND ((ti:(HIV OR AIDS OR PLHIV)) OR (ab:(HIV OR AIDS OR PLHIV)) OR (mh:(HIV OR AIDS OR PLHIV))) AND ((ti:(antirretroviral OR anti-retroviral OR antirretrovirais OR anti-retrovirais OR antiretroviral OR antiretrovirals OR antirretrovirales OR HAART OR ART)) OR (ab:(antirretroviral OR anti-retroviral OR antirretrovirais OR anti-retrovirais OR antiretroviral OR antiretrovirals OR antirretrovirales OR HAART OR ART)) OR (mh:(antirretroviral OR anti-retroviral OR antirretrovirais OR anti-retrovirais OR antiretroviral OR antiretrovirals OR antirretrovirales OR HAART OR ART))) AND ((ti:("Latin America" OR Latinoamerica OR Latin* OR "Central America" OR Centroamerica OR "Meso america" OR "Middle America" OR mesoamerica OR "South America" OR Sudamerica OR "America del sur" OR Caribbean OR Caribe OR Argentina OR Argentin* OR Bolivia* OR Brazil* OR Brasil* OR Colombia* OR Chile* OR Ecuador* OR Guiana OR Guyana OR Guayana OR Paraguay* OR Peru* OR Suriname OR Surinam* OR Uruguay* OR Venezuela OR Venez* OR Belize* OR "Costa Rica" OR "Costa Ric*" OR "El Salvador" OR Guatemala OR Guatemal* OR Honduras OR Hondur* OR Panama OR Panam* OR Mexico OR Mexic* OR Cuba* OR "Dominican Republic" OR "Republica Dominicana" OR Dominic* OR Haiti* OR Jamaica OR Jamaic*)) OR (ab:("Latin America" OR Latinoamerica OR Latin* OR "Central America" OR Centroamerica OR "Meso america" OR "Middle America" OR mesoamerica OR "South America" OR Sudamerica OR "America del sur" OR Caribbean OR Caribe OR Argentina OR Argentin* OR Bolivia* OR Brazil* OR Brasil* OR Colombia* OR Chile* OR Ecuador* OR Guiana OR Guyana OR Guayana OR Paraguay* OR Peru* OR Suriname OR Surinam* OR Uruguay* OR Venezuela OR Venez* OR Belize* OR "Costa Rica" OR "Costa Ric*" OR "El Salvador" OR Guatemala OR Guatemal* OR Honduras OR Hondur* OR Panama OR Panam* OR Mexico OR Mexic* OR Cuba* OR "Dominican Republic" OR "Republica Dominicana" OR Dominic* OR Haiti* OR Jamaica OR Jamaic*)) OR (mh:("Latin America" OR Latinoamerica OR Latin* OR "Central America" OR Centroamerica OR "Meso america" OR "Middle America" OR mesoamerica OR "South America" OR Sudamerica OR "America del sur" OR Caribbean OR Caribe OR Argentina OR Argentin* OR Bolivia* OR Brazil* OR Brasil* OR Colombia* OR Chile* OR Ecuador* OR Guiana OR Guyana OR Guayana OR Paraguay* OR Peru* OR Suriname OR Surinam* OR Uruguay* OR Venezuela OR Venez* OR Belize* OR "Costa Rica" OR "Costa Ric*" OR "El Salvador" OR Guatemala OR Guatemal* OR Honduras OR Hondur* OR Panama OR Panam* OR Mexico OR Mexic* OR Cuba* OR "Dominican Republic" OR "Republica Dominicana" OR Dominic* OR Haiti* OR Jamaica OR Jamaic*))).