



TREATMENT ADHERENCE AND FACTORS INFLUENCING ADHERENCE TO ANTIRETROVIRAL THERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: HIV/AIDS remains one of the world's most significant public health challenges. The goal of ART is to achieve maximal and durable suppression of virus replication. Adherence plays a very important role in success of antiretroviral therapy. **Objective:** to systematically assess the data of adherence and its influencing factors to antiretroviral therapy (if any) in HIV/AIDS patients. **Design:** systematic review and meta-analysis. **Material and methods:** PubMed/Medline and global health library database were used to search the literature. The major study characteristics were extracted i.e. study design, sample size, location and setting, adherence rate, etc. **Results:** There were ten cross-sectional studies enrolling 3657 participants. Treatment adherence found equal {OR:1.04(95% CI[0.875-1.246])} in both male and female and 0.6 times more {OR:0.67[95% CI(0.558-0.806)]} in age group less than 40 years as compare to age group more than 40 years. 54% {OR:0.56(95%CI[0.494-0.634])} of treatment adherence was found in the absence of most prevalent factors. **Discussion:** This systematic review and meta-analysis to summarize the data of ART adherence and factors influencing treatment adherence. **Conclusion:** Patients on ART face multiple barriers to adherence. Range of reasons for nonadherence to ART, including alcoholism, drug side-effects, long distance to travel to hospital, forgetfulness, etc.

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INTRODUCTION

HIV/AIDS remains one of the world's most significant public health challenges, particularly in low- and middle-income countries.^[1] HIV is a virus that attacks the immune system, AIDS is not a virus but a set of symptoms (or syndrome) caused by the HIV virus. This is the last stage of HIV and if left untreated will lead to death.^[2]

Globally, an estimated 36.7 million (34.0–39.8 million) people were living with HIV in 2015. An estimated 2.1 million (1.8–2.4 million) people were newly infected with HIV in 2015. An estimated 35 million people have died from HIV-related causes so far, including 1.1 million (940 000–1.3 million) in 2015. In mid-2017, 20.9 million people living with HIV were receiving antiretroviral therapy (ART) globally. Between 2000 and 2016, new HIV infections fell by 39%, and HIV-related deaths fell by one third while 13.1 million lives were saved due to ART in the same period.^[3] Achieving optimal therapeutic outcomes such as reduced viral load, reduction of drug resistance, and improved survival requires strict adherence to ART regimens.^[4] There is significant amount of research about the reasons behind poor adherence to antiretroviral therapy.

Adherence is a multidimensional concept that includes contextual, intrapersonal and behavioural factors. Recent research has found several barriers affecting adherence to ART.^[5]

METHOD

LITERATURE SEARCH

A systematic literature search was performed in the following electronic bibliographic databases: PubMed/ MEDLINE and the Global Health Library for all publications up to March 2018. Search terms composed of combined text: “Adherence,” “Patient Compliance,” “antiretroviral therapy,” “HIV,” “AIDS”, “contributory factors” for all years. No restriction based on year of publication, study design or language was applied. Given the comprehensive approach of the search, references were not checked, except those from a recent global systematic review.

Inclusion criteria

Studies that given the quantitative data for adherence factors included. Review articles, policy documents and adherence training manuals were excluded.

Study selection and data extraction

Initially, 98 studies were searched on the basis of title and then after reviewing all the studies independently final 10 studies

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were selected as per the inclusion criteria [figure 1]. Initial search was 98 studies and then 49 studies were excluded based on criteria i.e. not given the quantitative data about the adherence to the Anti-retroviral therapy. After the reviewing the titles of the study 49 studies were retrieved. In the 49 retrieved articles, twenty-four studies were removed (seven duplicated studies; eight review article and nine abstracts). The final retrieved articles were twenty-five, in that 15 studies were excluded after full review of the studies.

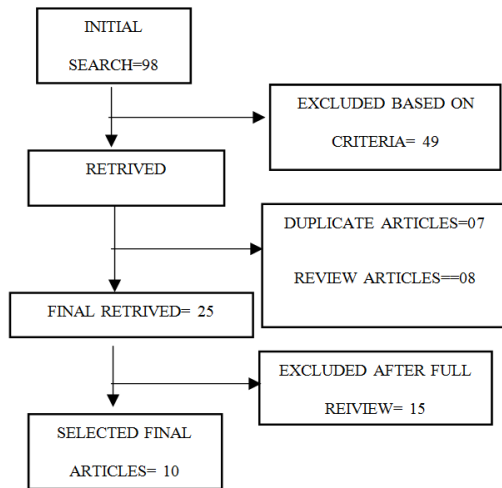


Figure 1 Flow-chart

Final selection of 10 studies and for the data extraction full review of the articles were done. Data were extracted on study design, sample size, study setting, adherence rate, non-adherence rate and non-adherence factors, etc. The metaanalysis was done by using IBM SPSS Statistic 20 software. For the purpose of meta analysis, collected the proportion data and quantity data.

RESULTS

Identification of studies

The following flow chart showing the systematic selection process of the studies. Through the initial search 98 studies were identified, then 49 studies were excluded according to the inclusion criteria. After the 49 studies were retrieved, in that 8 studies were duplicate; 7 studies were review based articles and 9 studies were abstracts. Accordingly, 10 studies met the inclusion criteria and were included in the systematic review.

Characteristics of included studies

The characteristics of the selected studies are shown in table 1. The total 10 studies enrolled total 3657 participants (1815 males and 1842 females). The average sample size was 350.25. The mean age was 37.05+-14.5 years. These ten studies followed cross sectional method of the research design.

Table 1 Study characteristics & Treatment adherence

Author	Study conducted year	Location & Setting	Study Design	Sample Size	Mode of Information collected	Adherence Rate	Non-adherence Rate	Odd ratio [calculated for meta-analysis]
Shukla <i>et al</i> ^[6]		ART center of two tertiary care hospitals in Uttar Pradesh, India	cross-sectional, analytical study.	322	Pill count method, pretested and structured questionnaire and Becks Depression Inventory (Hindi)	89.1%	10.9%	Age: 0.92 [95% CI (0.452-1.866)] Gender: 1.66 [95% CI (0.821-3.364)]
Gokarn, <i>et al</i> ^[7]	November 2007 and September 2009	Aurangabad, India	cross sectional observational study	300	Morisky Medication Adherence Scale (MMAS)	96.60%	3.40%	Age: 2.342 [95% CI (1.008-5.441)] Gender: 0.72 [95% CI (0.408-1.282)]
Saha, <i>et al</i> ^[8]	2011	ART centre of a tertiary care hospital in West Bengal, India	observational, analytical, cross-sectional epidemiological study	370	the Adult AIDS Clinical Trial Group adherence questionnaire	87.60%	12.40%	Age: 6.17 [95% CI (1.461-26.092)] Gender: 1.33 [95% CI (0.72-2.478)]
Banagi Yathiraj, <i>et al</i> ^[9]	April 2014 to April 2015	tertiary care hospitals, at Mangalore, Karnataka, India	cross-sectional study	409	pretested semi structured questionnaire	70.40%	29.60%	Age: 1.18 [95% CI (0.770-1.822)] Gender: 0.47 [95% CI (0.293-0.750)]
Aye, <i>et al</i> ^[10]	2016	an HIV outpatient clinic, Mon state, Myanmar	cross-sectional study	300	Structured interview questionnaire And visual analogue scale	84%	16%	Age: 1.28 [95% CI (0.689-2.377)] Gender: 0.60 [95% CI (0.324-1.125)]
Kim MH <i>et al</i> ^[11]	2012	HIV clinics in central and south-eastern Malawi.	cross-sectional study	519	Structured interview questionnaire	55%	45%	Gender: 1.1 [95% CI (0.751-1.609)]
Abera <i>et al</i> ^[12]	2015	JUTH, located in Jimma town, Oromia	cross-sectional study	221	Structured closed ended questionnaire	63.8%	36.19%	Age: 0.62 [95% CI (0.342-1.105)] Gender: 0.78 [95% CI (0.434-1.394)]
Mitiku <i>et al</i> ^[13]	2010	Ethiopia	cross-sectional study	239	standard interview questionnaire	87%	13%	Age: 0.56 [95% CI (0.253-1.219)] Gender: 0.86 [95% CI (0.372-1.976)]
Letta <i>et al</i> ^[14]		Harar and Dire Dawa towns, Ethiopia	cross-sectional study	620	structured questionnaire with a face-to-face interview	85%	15%	Age: 0.91 [95% CI (0.583-1.428)]
Alagaw <i>et al</i> ^[15]	2012	Wolaita Soddo Hospital, Southern Ethiopia	cross sectional study	357	Self- report	74.4%	25.6%	Age: 1.23 [95% CI (0.599-2.42)] Gender: 1.61 [95% CI (0.843-3.092)]

The study by Shukla *et al* used unique data collection instruments designed by their respective study groups and used and Becks Depression Inventory (Hindi) for method of data collection.^[6] The study by Gokarn *et al* used Morisky Medication Adherence Scale (MMAS) and self-designed questionnaire for data collection.^[7] The study by Saha *et al* used the Adult AIDS Clinical Trial Group adherence questionnaire while Banagi Yathiraj *et al*, Aye *et al*, Kim AH *et al*, Abera *et al* and Letta *et al* used data collection instruments designed by their respective study groups whereas the study by Mitiku *et al* used the standard interview questionnaire and Alagaw *et al* used self-report from patient as data collection instrument.^[8-15]

All the studies reported the adherence and non-adherence rate.

The seventy percentage of studies (7/10) reported the range of ART. The seventy percentage of studies (7/10) reported the recall period for the data collection while Only one (1/10) study reported First line and second line ART regimen and other studies had not reported the specific ART regimen. Hundred percentage of studies reported the qualitative and quantitative data related to factor influencing the treatment adherence while eighty percentage of studies (8/10) percentage of the studies reported the definition of adherence in own words.

Reasons for non-adherence

The reasons for non-adherence to ART across the included studies are summarized in Table 2.

Table 2 Treatment Adherence & contributory factors

Study	Definition of adherence	Treatment regimen	Range of ART [calculated Odd ratio for metaanalysis]	Recall period	Adherent participant N (%)	Reasons for non-adherence (most 3 prevalent)
Shukla <i>et al</i> ^[6]	a patient’s ability to follow a treatment plan, take medications at prescribed times and frequencies, and follow restrictions regarding food and other medications.	Antiretroviral therapy (specific regimen not reported)	6 months OR: 10.26 [95%CI (4.793-21.975)]	Not reported	287 (89.1%)	1. busy with other work 2. felt sick or ill 3. Don’t have money to visit ART center
Gokarn, <i>et al</i> ^[7]	the ability to take prescribed drugs in the recommended dosages and schedules and following any special instructions e.g. empty stomach, after meals etc. >95 %.	Antiretroviral therapy (specific regimen not reported)	6 months	Not reported	290 (96.60%)	1. Were out of home/were traveling 2. Too busy in other work 3. side effects of medication
Saha, <i>et al</i> ^[8]	a self-report of not missing a single dose of medication over the previous four days.	Antiretroviral therapy (specific regimen not reported)	6 months OR: 1.15 [95% CI (1.102-1.19)]	Four days	370 (87.60%)	1. forgetting to take medicine 2. being away from home 3. busy with other things
Banagi Yathiraj, <i>et al</i> ^[9]	Not reported	Antiretroviral therapy (specific regimen not reported)	Not reported	30 days	288 (70.40%)	1. forgetfulness to take ART 2. Alcohol intake
Aye, <i>et al</i> ^[10]	Adherence is the extent to which a person is taking the medicine as prescribed by physician and according to medical recommendations, inclusive of timing, dosing and consistency and correctly taking the drugs in terms of right doses, right times and following the dietary recommendations	Antiretroviral therapy (specific regimen not reported)	1 month OR: 0.86 [95% CI (0.461-10596)]	30 days	252 (84%)	1. busy with other things 2. away from home 3. forgetfulness
Kim MH <i>et al</i> ^[11]	Self-efficacy for antiretroviral adherence is one’s sense of being able to adhere to ART as prescribed	First line and second line ART regimen	Not reported	7 days, 30 days and 6 months	366 (55%)	1. forgetting 2. travel from home 3. busy with other things
Abera <i>et al</i> ^[12]	The extent to which the patient continues the agreed upon mode of treatment under limited supervision when faced with conflicting demands as distinguished from compliance or maintenance	Antiretroviral therapy (specific regimen not reported)	Not reported	Not reported	141 (63.8%)	1. forgetting 2. traveling 3. being busy
Mitiku <i>et al</i> ^[13]	Not reported	Antiretroviral therapy (specific regimen not reported)	1 month OR: 1.28 [95% CI (0.352-4.696)]	7 days	208 (87%)	1. forgetting 2. some due to travelling 3. few due to being busy
Letta <i>et al</i> ^[14]	ART adherence was defined as taking all pills in correctly prescribed doses at right time (no dose missed or delayed for greater than or equal to 90 min)	Antiretroviral therapy (specific regimen not reported)	3 months	7 days	527 (85%)	1. forgetting 2. being away from home 3. being busy with different activities
Alagaw <i>et al</i> ^[15]	Adherence was measured by dose adherence; adhered were those who took greater than or equal to 95% of the prescribed drugs	Antiretroviral therapy (specific regimen not reported)	1 month	7 days	312 (74.4%)	1. forgetting 2. Stock finished 3. lack of transport cost,

Eighty percentage (8/10) studies showed that being busy with other works and simply forget to take medicine were the most prevalent reasons for non-adherence to ART. Other common obstacles for non-adherence was away from home showed in forty percentage (4/10) studies. The studies also reported travelling cost, feeling sick, medicine not available at centre, substance abuse were the factors that affect the adherence to the treatment. In Table 2 odd ratio for ART regimen calculated for individual study, finding revealed that adherence seen in long time duration treatment. In table 1 odd ratio for age and gender were calculated, the findings revealed in most of study treatment adherence seen in less than 40 years of age group and more in men than females.

DISCUSSION

This systematic review and meta-analysis to summarize the data of ART adherence. By the literature reviewing, found the various studies that helped to understand the adherence to the ART regimen as well as the non-adherence factors also. The Average adherence rate was 79.29% among all studies. Treatment adherence among age less than 40 years was 0.6 times more as compare to age group more than 40 years while treatment adherence is equal in both female and male among all these studies. Pooled analysis of all studies pooled estimate treatment adherence found equal {OR:1.04(95% CI[0.875-1.246])} in both male and female and 0.6 times more {OR:0.67[95% CI(0.558-0.806)]} in age group less than 40 years as compare to age group more than 40 years. 54% {OR:0.56(95%CI[0.494-0.634])} of treatment adherence was found in the absence of most prevalent factors. If the patients were disclosed their condition it lead more adherence of treatment (OR 1.6[95% CI (0.671-4.205)]).

The study by Shukla *et al* revealed no difference in male and female treatment adherence. According to the results persons who were busy with other works were non-adherence (40.0%) to antiretroviral therapy. Apart of these most prevalent factors for non-adherence were forget to take medicine and being away from home.^[6] The study by Gokarn *et al* Adherence rate of >95% was reported by 290 (97%) patients. On MMAS scale 78% of the patients were found adherent to the treatment. On multivariate analysis factors such as age, addictions, difficulty in remembering treatment, finding treatment to be difficult, taking traditional medicines and having no one to remind about medicines were found to be associated with non-adherence. The most common reason for non-adherence were missing pills while travelling or being out of home.^[7] The study by Saha *et al* total of 87.6% of patients were found to be adherent to HAART. Principal causes of non-adherence were forgetting to take medicine (70.2%), being away from home (65.2%), and busyness with other things (64.7%). Multivariate logistic regression analysis revealed that non-adherence was significantly associated with a positive family history of HIV/AIDS (odds ratio [OR] 16; 95% confidence interval [CI] 2.2–114.3; $p = 0.01$), occurrence of side effects with HAART (OR 9.81; 95% CI 1.9–51.7; $p = 0.01$) and employment (OR 5.93; 95% CI 1.5–23.2; $p = 0.01$).^[8] The study by Banagi Yathiraj *et al* among 409 PLHIV, 70.4% showed adherence to ART (>95%). Univariate analysis yielded many factor associated with adherence ($P < 0.05$). However, on multivariate analysis, PLHIV who do not forget to take ART and not consuming alcohol were the factors consistent with adherence to ART ($P < 0.05$).^[9] The study by Aye *et al* Among

300 patients (male 37.7% and female 62.3%, with a mean age of 41.3 years, standard deviation 8.7), 84% reported $\geq 95\%$ adherence to ART in the past month. Among 16% of those reporting non-adherence, major reasons for skipping the medication were being busy (23%), being away from home (17.7%) and being forgetful (12.3%). In multivariable logistic regression, low behavioural skills on ART adherence (OR = 0.31, 95% CI: 0.10-0.94), tobacco use (OR = 3.22, 95% CI: 1.28-8.12), having disclosed their HIV status (OR = 0.07, 95% CI: 0.01-0.69), having a partner who was not on ART (OR = 4.25, 95% CI: 1.70-10.64) and among men, having erectile dysfunction (OR = 15.14, 95% CI: 1.41-162.66) were significant associated with ART non-adherence.^[10] The study by Kim H *et al* The mean age of participants (SD) was 14.5 (2) years and 290 (56%) were female. Of the 519 participants, 153 (30%) reported having missed ART doses within the past week, and 234 (45%) in the past month. Commonly reported barriers to adherence included forgetting (39%), travel from home (14%), busy with other things (11%), feeling depressed/overwhelmed (6%), feeling stigmatized by people outside (5%) and within the home (3%). Factors found to be independently associated with missing a dose in the past week were drinking alcohol in the past month (OR 4.96, 95% CI [1.41–17.4]), missed clinic appointment in the past 6 months (OR 2.23, 95% CI [1.43–3.49]), witnessed or experienced violence in the home (OR 1.86, 95% CI [1.08–3.21]), and poor treatment self-efficacy (OR 1.55 95% CI [1.02–2.34]). Sex and age were not associated with adherence.^[11] The study by Abera *et al* pooled analysed the total 221 participants more than half 153 (69%) were greater than 30 years, 144 (65.15%) were females, 167 (75.56%) were urban dwellers, 169 (76.43%) were Oromo ethnic group. Overall from the study participants 80 (36.19%) had poor adherence and 141 (63.8%) had good adherence to their ART treatment. Factors like educational status, residence, occupation and alcohol addiction are significantly associated with the level of adherence to ART treatment.^[12] The study by Mituku *et al* depicted the result that among the 239 study participants, the magnitude of adherence to ART in the week before interview was 87%. The main reasons for non-adherence were forgetting (47.2%), traveling (18.9%), and being busy doing other things (15.1%). There was not any independent predictor identified for adherence to ART.^[13] The study by Letta *et al* revealed The level of ART adherence was 85%. Adherence was more likely among patients of 35–44 years (AOR=2.39; 95% CI=1.15–5.01), had monthly income of 501.00–999.00 Ethiopian Birr (ETB) (AOR=6.73; 95% CI=2.71–16.75), no history of opportunistic infection (AOR=2.81; 95% CI=1.47–5.36), and had good family support (AOR=2.61; 95% CI=1.45–4.72). However, those who did not disclose their sero-status (AOR=0.45; 95% CI=0.21–0.97) and did experience depression (AOR=0.36; 95% CI=0.21–0.61) were less likely adherent than their counterparts.^[14] The study by Alegaw *et al* used Multi-method adherence assessment consisting of self-report, monthly dispense schedule and dietary requirements, were used to measure adherence and the average adherence rate was 74.4%. Multivariate logistic regression analysis showed that, with whom a subject lives (Adjusted Odds Ratios (AOR)=4.943,1,(2.168-11.270)), depression (AOR=2.221,1,(1.093-4.515)), and having inadequate diet to take with ART (AOR=2.229,1,(1.034-4.807)), were independent predictors of dose adherence.^[15]

There are a range of reasons for failing to adhere to ART, including drinking alcohol, having drug side-effects, long distance to travel to hospital, being illiterate, non-disclosure of HIV status, being female, lack of knowledge and negative perceptions towards ART. The key reason for skipping ART given was travel fare problems presumably in order to collect ART, followed by pill running out and wanting to avoid the side-effects.

CONCLUSION

It is mandatory to achieve hundred percentage adherence to antiretroviral therapy by following the treatment regimen strictly. For adherence, it is necessary to timely detection of patient behaviour as well as the physical condition of the patient. Reduce the factors that can affect the treatment adherence to antiretroviral therapy. Adherence is a process, not a single event, and adherence support must, therefore, be integrated into regular clinical follow-up. This systematic review concludes that most prevalent factors for non-adherence were being busy with other works, forgetfulness, away from home, feeling sick, etc. These could be minimizing by the health care members as well as patients and family members.

Implication to nursing practice

The primary goal of treatment with ART is to prevent HIV-related morbidity and mortality. Many studies have shown a strong correlation between adherence and clinical outcomes and/or laboratory markers (notably CD4 count). Non-adherence has been found to diminish the immunological benefit of ART and increase AIDS-related morbidity, mortality, and hospitalizations. Treatment adherence is generally regarded as an important factor in achieving optimal outcomes across many disease states; in the treatment of HIV, poor adherence to treatment has the potential to impact outcomes on multiple levels. Poor adherence to antiretroviral therapy (ART) is associated with less effective viral suppression, which risks the immediate health of the patient, but also risks creating permanent treatment resistance to that particular agent or group of agents within a given combination therapy regimen. This may have downstream effects on treatment costs as well as therapeutic options. The causes of poor adherence to ART are extremely diverse, and include complexity of therapeutic regimens (eg, pill burden and dosing frequency), treatment side effects, poor health literacy, poor patient-physician relationship, and limited access to ART as a result of formulary restrictions or copayment costs. Treatment approaches, such as the use of fixed-dose combinations of ART agents to reduce dosing complexity, as well as educational interventions, such as medication therapy management initiatives, have been shown to improve adherence to therapy in HIV. It is important that all members of the healthcare team address potential barriers to adherence in order to achieve viral suppression and optimize outcomes in patients with HIV. Priorities should be given to improving adherence by providing regular follow-up, increasing patients' awareness of the ART treatment, including its benefits and side-effects, eliminating problems of access and alleviating the impact of cost.

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